Viruses Associated With Pneumonia in Adults

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Viral pneumonia, which is typically associated with disease in childhood, is increasingly recognized as causing problems in adults. Certain viruses, such as influenza virus, can attack fully immunocompetent adults, but many viruses take advantage of more-vulnerable patients. The latter include patients receiving immunosuppressive therapy and elderly subjects, particularly those residing in long-term care facilities. The range of viruses producing pneumonia in adults includes common agents, such as varicella-zoster virus and influenza virus, as well as respiratory syncytial virus, human metapneumovirus, adenoviruses, picornaviruses, and coronaviruses. The roles played by other agents, such as rhinoviruses and human bocaviruses, in pneumonia are still under study. While therapy for most of theses agents, at least in adults, has not yet been fully clarified, it is reasonable to assume antivirals may work in certain situations if they are introduced early enough in the course of infection.

It is estimated that 100 million cases of viral pneumonia occur each year [1]. Recent reports suggest that the etiology of many of these may now be identified [2–4] using culture, serologic analysis, antigen identification, or newer molecular techniques [2–5]; however, the attribution of the pneumonia to viruses can be difficult because viruses may be found in respiratory secretions after aspiration from the upper airways or after asymptomatic viral shedding. Further, coinfection with 2 organisms may occur. Research will have to clarify the role of some of these agents, using techniques to demonstrate viral proliferation or viral components in lung parenchyma. Determination of high viral loads in respiratory specimens can be useful in this regard, but few studies have reported viral loads, and these may vary with the patients age, timing of the specimen, and the type of specimen. Standards for viral loads will need to be clarified. The following report summarizes the viruses that have been associated with pneumonia in adult patients.

Received 28 November 2011; accepted 24 February 2012; electronically published 15 March 2012.

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Clinical Infectious Diseases 2012;55(1):107–13

DOI: 10.1093/cid/cis297

INFLUENZA

Epidemics of influenza appear to have occurred from ancient times, but literature about the disease dates largely from the epidemic of 1918–1919, although influenza virus was not isolated until 1933 [6]. Louria et al. [7] were perhaps the first to clarify the nature of pneumonia during the influenza epidemic of 1957–1958. They separated primary influenzal pneumonia from bacterial pneumonia occurring in the wake of influenza and mixed viral-bacterial pneumonias. Louria et al. identified 6 adult patients they felt had pneumonia due to influenza virus on the basis of virus isolation or serologic criteria and absence of significant bacteriologic findings. Five of the 6 patients died. During the same epidemic, Martin et al. [8] identified 32 fatal cases of influenza, 29 of which occurred in patients aged ≥15 years. Eleven patients in this study were classified as having influenza without bacterial complications, including 4 with pneumonia or perihilar congestion. Oseasohn et al. [9] reported 33 fatal cases of Asian influenza, of which 9 were associated with "sterile cultures" and at least 1 involved apparent primary influenzal pneumonia, and Kaye et al. [10] described 3 cases attributed to influenza virus pneumonia.

Additional cases of influenzal pneumonia were reported following the epidemic of 1968. Lindsay et al. [11] described 20 patients aged ≥15 years with pneumonia

and influenza; 6 died, of whom 5 had typical histologic findings of primary influenzal pneumonia. Burk et al. [12] reported 4 adult cases of pneumonia during that epidemic, one of which appeared to have pneumonia due to the epidemic virus.

Noble et al. [13] reported a case of influenza pneumonia documented by lung biopsy findings. The biopsy specimen from this case was culture positive for influenza A virus, and all bacterial and fungal cultures of the biopsy specimen were negative, suggesting that this was pneumonia attributable to influenza virus. The biopsy contained evidence of necrotizing bronchitis and bronchiolitis. The bronchial epithelium was eroded, and alveoli contained prominent hyaline membranes, edema fluid, and red blood cells, with mild interstitial inflammation.

Following episodic reports of pneumonia associated with H5N1 avian influenza virus [14], a swine influenza pandemic occurred in 2009 [15], during which the rate of hospitalization reached 7% [16] and the rate of pneumonia was reported as 0.4% [16]. Publications detailed viral pneumonia associated with the swine virus and allowed comparisons with seasonal influenza [16–20]. Common features of influenza were fever and cough [15], and patients developing pneumonia often complained of dyspnea. The interval between onset of symptoms and hospitalization usually was 2–6 days. Overall, 28% of hospitalized patients were admitted to intensive care units (ICUs) [21, 22], and 12%–59% developed adult respiratory distress syndrome [23, 24]. Mortality due to viral pneumonia reported in these studies ranged from 20% to 25%. Patients at risk for severe outcomes from swine influenza in 2009 included those with cardiac disease, pulmonary disease, or diabetes mellitus.

Frequent radiographic signs of influenzal pneumonia included patchy bilateral lower lobe infiltrates or interstitial infiltrates [25, 26]. Lactic dehydrogenase levels were often raised in patients with influenzal pneumonia [26].

Pregnancy was associated with an increased risk of H1N1 pneumonia, and rates 4–9 times greater than those of the general public were reported [21, 23]. Pneumonia occurred in all trimesters, as well as in the postpartum period [24], but the incidence was greatest in the third trimester [17]. Mortality in this group was comparable to that in the general public [27, 28].

The pathology of primary influenzal pneumonia is characterized by capillary thrombosis, focal necrosis of the alveolar wall, development of hyaline membranes in alveoli, alveolar edema, hemorrhage, necrotizing bronchitis, and bronchiolitis (Figure 1) [29, 30]. Several studies have improved our understanding of this disease process. Higher viral loads have been found in some patients with a fatal outcome from H5N1 influenza. To et al. [31] have shown that the viral load was slower to decline in cases of acute respiratory distress syndrome due to H1N1 influenza virus and that interleukin 6, interleukin 10, and interleukin 15 levels were elevated in the plasma of these patients.

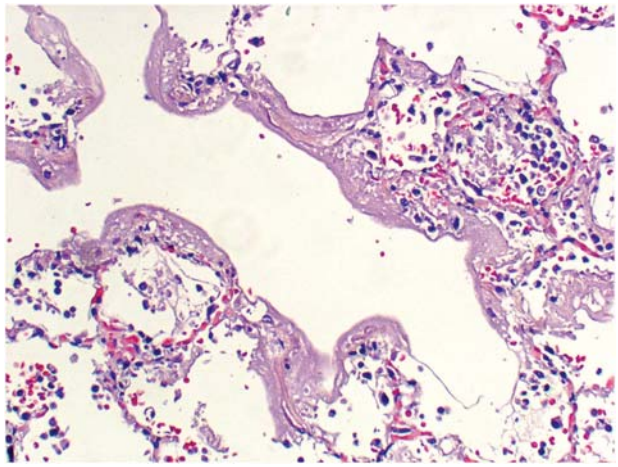

Figure 1. Lung biopsy specimen from a patient with influenzal pneumonia, showing numerous necrotic cells in alveolar spaces, hyaline membranes, destruction of bronchial walls by neutrophils, and intra-alveolar hemorrhage, as well as occasional streptococcus pneumonia in alveolar spaces (kindly provided by Dr Fritz Lin, UCI Department of Pathology).

ADENOVIRUSES

Adenoviruses include >50 serotypes, but only about one-third are associated with human disease. More than 80% of infections, including pneumonia, associated with these viruses occur in children, especially those <4 years old, but they account for 1%–7% of adult respiratory infections [32]. In military recruitment centers [33, 34], febrile respiratory disease is common, and cases of pneumonia have been reported [35]. Pneumonia cases in recruits were milder, were preceded by upper respiratory tract symptoms, and included rales and rhonchi on auscultation, leukocyte counts that were not elevated, and infiltrates on chest radiographs that were patchy and irregular or reticular. Resolution occurred in all 12 military patients described by Bryant and Rhoads [35]. However, Dudding et al. [36] reported fatal outcomes for 3 other trainees with adenoviral pneumonia. Recent reports have included adults who were immunosuppressed and experienced disastrous consequences from adenoviral pneumonia [37], but reports of adenovirus pneumonia in immunocompetent adults have also been published, as reviewed by Clark et al. [38]. These authors found 19 articles reporting on 21 immunocompetent patients with adenoviral pneumonia. The mean age of these patients was 40 years, and fever (90%), cough (81%), and dyspnea (71%) were frequent. The median leukocyte count was 7.7 cells/mm^3, but 52% of patients were lymphopenic. The most common radiograph finding was bilateral interstitial markings. Pneumonia due to adenovirus has also been reported in closed populations of adults [39].

A strain of adenovirus first identified in Dutch military recruits in 1955 has become a predominant circulating serotype. Tate et al. [40] reported the occurrence of this serotype in a US Air Force training facility. Twenty-three of 551 infected trainees were hospitalized with pneumonia, and 1 died. Lewis et al. [41] described an outbreak of adenovirus serotype 14 among civilians in Oregon with a median age of 51.9 years. Of a total of 67 cases, 29 were hospitalized; 26 of the hospitalized patients had abnormal chest radiograph findings, of whom 10 (38%) had infiltrates involving >1 lobe. Eighteen patients required critical care, and 7 (18%) patients died. Similarly, Esposito et al. [42] reported an outbreak of adenovirus serotype 14 infection on an island in southeast Alaska. Among 32 cases of pneumonia (median age, 47.5 years), they found 18 confirmed and 3 probable cases due to serotype 14. Pneumonia in 10 patients progressed to severe disease, and 1 died.

CORONAVIRUSES

Coronaviruses may also produce pneumonia in adults. In 2003, the epidemic of severe acute respiratory syndrome (SARS) [43–45] emerged. SARS coronavirus infection was first detected in Guangdong province in China but spread to Hong Kong, Vietnam, Singapore, and Canada. Patients presented with fever, myalgias, malaise, chills, and cough [45]. Dyspnea and pleuritic pain came later, sometimes with diarrhea. Lymphocytopenia was common. Other findings occasionally seen included thrombocytopenia and increased levels of D-dimers and liver enzymes. Between 60% and 100% of patients had abnormal findings on initial chest radiographs, with ground-glass opacities seen most commonly. Between 20% and 30% of patients required admission to the ICU, with most needing mechanical ventilation. The overall case-fatality rate approximated 10%, with a worse burden among patients aged >65 years (mortality, 50%). Children aged <12 years tolerated the virus better.

Other coronaviruses have been shown to cause pneumonia in adults. Woo et al. [46] found coronavirus HKU 1 in nasal washings from 10 of 418 patients with pneumonia; 9 who tested positive were adults. The median age of the 10 patients was 71.5 years; 8 had underlying disease, and 2 died. The disease was indistinguishable from community-acquired pneumonia due to other agents. Falsey et al. [47] evaluated 100 older adults hospitalized with cardiopulmonary illness and found 8 patients infected with coronaviruses; 5 had coronavirus 229E, and 3 had coronavirus OC 43. Two patients with coronavirus infections had pneumonia. All patients had significant underlying disease, but all recovered. Johnstone et al. [48] reported that 4 of 193 adult patients admitted to the hospital with community-acquired pneumonia were infected with coronavirus OC 43.

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is also significant cause of pneumonia in adults. Dowell et al. [49], in a study of patients admitted to the hospital for community-acquired pneumonia, reported that RSV was the third most common cause of community-acquired pneumonia in hospitalized patients, behind *Streptococcus pneumonia* and influenza virus. Johnstone et al. [48] reported that RSV was responsible for 2.6% of community acquired-pneumonia cases in adults. Thompson et al. [50] estimated that, between the 1990–1991 and 1998–1999 pneumonia seasons, RSV was associated with 2707 deaths annually; 78% of deaths related to respiratory/circulatory problems occurred in people aged >65 years.

The clinical features of RSV infection in hospitalized patients included nasal congestion, dyspnea, and wheezing. Cough was nearly universal. Twenty percent of these patients had pneumonia. Dowell et al. [49] also noted that wheezing was more frequent in RSV pneumonia patients than in patients with pneumonia due to other causes, as was the presence of rhonchi and nonelevated white cell counts. Radiographically, the infiltrates associated with RSV pneumonia were often small, focal, and unilateral, although Dowell et al. [49] had patients with pneumonia with infiltrates reported to be lobar in distribution.

Falsey et al. [51] reported that the death rate for elderly hospitalized patients with RSV infection was 10%; mortality specifically associated with pneumonia was not noted. Risk factors for severe infection included underlying chronic pulmonary disease and low serum neutralizing antibody levels [52] and, for respiratory failure, included concurrent cardiopulmonary disease and high nasal viral loads.

Outbreaks of RSV infection have occurred in long-term care facilities, with high attack rates and high death rates [53]. RSV infection is a significant risk for bone marrow transplant recipients and patients with leukemia, among whom mortality rates have approximated 50%.

HUMAN METAPNEUMOVIRUS

Human metapneumovirus (HMPV) is closely related to RSV. By the age of 25 years, everyone has been infected with this agent, but during early life, infections result in incomplete immunity, allowing for recurrent infections.

In adults, Walsh et al. [54] sought HMPV in 1386 hospitalized patients. They found 91 patients infected with HMPV alone and 27 dually infected with HMPV and a second agent. Among 91 hospitalized patients, 23 developed pneumonia, 12 needed transfer to the ICU, 11 needed ventilator support, and 6 died. The average age of patients who died was 85 years. Details about the pneumonia cases were not provided. Johnstone et al. [55] prospectively studied patients with pneumonia

who were admitted to 5 Edmonton, Canada, hospitals. They identified 193 patients with adequate nasopharyngeal samples for testing, including 8 patients with pneumonia due to HMPV. All 8 had comorbid cardiac or pulmonary disease, and all had cough, but only 1 had fever. Most had dyspnea with low oxygen saturations, all had normal white cell counts, and all but 1 were lymphocytopenic. Fifty percent had pneumonia involving >1 lobe, and 3 had bilateral infiltrates. There was no ICU admission in the group and no deaths. Hamelin et al. [56] found that 6 of 145 patients who had chronic obstructive pulmonary disease and pneumonia and were admitted to the emergency department in Quebec, Canada, over 2 winter/spring seasons were infected with HMPV.

Like RSV, HMPV can also cause outbreaks in long-term care facilities. Boivin et al. [57] reported that 96 of 364 residents of a long-term care facility developed respiratory disease over a 6-week period. There were 6 confirmed infections with HMPV in the group, and 3 infected patients died with pneumonia. Real-time polymerase chain reaction (PCR) of an autopsy specimen from a 29-year-old female revealed HMPV in her bronchial epithelium. Louie et al. [58] also described an outbreak in a long-term care facility, where 26 of 171 residents were infected and 8 developed pneumonia, including 2 who were hospitalized and 1 who died. The mean age of these patients was 70 years. Honda et al. [59] reported a similar outbreak from Japan.

HMPV has also been reported to cause pneumonia in immunocompromised patients [60, 61]. Like RSV, ribavirin has in vitro activity against this virus [52].

OTHER AGENTS

Parainfluenza viruses also cause disease in children, but occasional examples of these same viruses producing pneumonia in both immunocompetent and immunoincompetent adults have been reported. Wenzel et al. [62] described 3 US Marine recruits with pneumonia and serological evidence of parainfluenza virus type 1 infection and 2 US Marine recruits with pneumonia and serological evidence of parainfluenza virus type 3 infection. All of the recruits were febrile, and 2 had modest elevations in their white cell counts. Marx et al. [63] described 1 patient with lobar pneumonia who had serological changes compatible with infection with parainfluenza virus type 1 infection and no other organisms isolated. An adult with pneumonia attributed to parainfluenza virus type 3 was described by Cunha et al. [64]. The patient had patchy interstitial infiltrates, was febrile, and had evidence of leukocytosis and relative lymphopenia. Parainfluenza virus type 3 pneumonia has also been reported in a patient who underwent hematopoietic stem cell transplantation [65].

Gremillion and Crawford [66] reported on 106 US Air Force recruits with measles virus pneumonia. This constituted 3.3% of 3220 measles cases seen over a 42-month period. The illness in these patients was characterized by high fevers, long hospital stays, and interstitial infiltrates, with pure viral infections. Bacterial superinfections in the lungs (in 30% of cases), sinuses, and ears were common. Liver function abnormalities were also common, but none of these patients died. Measles virus pneumonia appears 3 times more frequently in pregnant women with the disease [67] and, in immunocompromised patients, may occur as giant cell pneumonia.

Enteroviruses, including coxsackieviruses and rhinoviruses, have also been reported to be associated with pneumonia in adults. Hayden [68] reviewed the evidence that rhinoviruses can replicate in the lower respiratory tract. Hohenthal et al. [69], in a study of 231 cases of community-acquired pneumonia, found 5 cases where enteroviruses were the only agents found and 2 where rhinoviruses were the only agents identified. Recently, Legay et al. [70] reported on a 76-year-old male with a fatal case of pneumonia in which coxsackievirus A 16 was identified by PCR from bronchoalveolar lavage fluid, serum, and pharyngeal secretions. There was an associated 8-fold rise in antibody titer. Ghosh [71] described 4 adult patients who had significant myelosuppression following blood and marrow transplantation and also developed rhinovirus infection and fatal pneumonia. No other pathogens, save rhinoviruses, were isolated from these 4 individuals, and interstitial pneumonitis was found at autopsy.

Human bocaviruses are novel parvoviruses isolated from 2%–19% of samples taken from patients, especially children, with acute respiratory disease [72] and has also been found in blood. Primary human bocavirus infection can be followed by a long period of viral shedding frequently associated with other agents. Its exact role in producing respiratory disease is under investigation. Fry et al. [73] studied 1171 patients in Thailand who had signs and symptoms of pneumonia underwent chest radiography. Four of these patients with pneumonia were aged ≥65 years and had human bocavirus infection, including 2 from whom these were the only agents detected.

Varicella-zoster virus is known to produce pneumonia, especially in adults. In a review by Triebwasser et al. [74], pneumonia was reported to occur in 14% of adults with varicella-zoster virus infections who were serving in the US Air Force. The most frequent radiographic finding in adults with chicken pox–associated pneumonia was a nodular infiltrate, often with peribronchial distribution. Hypoxemia was common. White cell counts were usually normal, and most patients were febrile. The mortality rate for chicken pox–associated pneumonia in adults before effective chemotherapy was reported to be 10%–30%.

Herpes simplex virus (HSV) is also known to cause pneumonia, but chiefly in immunocompromised patients. Shah and Chemaly [75] reviewed the occurrence of this disease in patients

with hematologic malignancies, noting that many of the pneumonias attributable to this virus occurred in this setting. Most of the patients they reviewed were infected with HSV type 1 and experienced reactivation of the virus. Findings often involved low-grade fever, cough, dyspnea, and wheezing. Hypoxia was common, sometimes requiring the use of ventilators. Radiographic findings were nonspecific, but ground-glass-appearing lesions were commonly seen on computed tomographic scans of the lungs in this group. Ramsey et al. [76] also reported on 17 adult patients (age, ≥17 years) with hematologic problems, all but one of whom underwent bone marrow transplantation. All transplant recipients had pneumonia, all 17 patients had postmortem lung cultures that were positive for HSV, and 15 patients had histologic evidence of HSV in the lungs. Other infections occurred concomitantly in all but 4 of the patients.

Cytomegalovirus is known to cause pneumonia in immunosuppressed patients, especially bone marrow transplant recipients [77], but because of the unique nature of the disease and the constraints of space, this virus will not be reviewed here. Epstein-Barr virus has been associated with pneumonia, as reported by Siskandan et al. [78], who detected the virus in lung tissue, using riboprobes. Hantavirus may cause a pneumonic picture [79] due largely to the presence of interstitial edema, and recent reports have suggested that mimivirus and parechoviruses may be associated with pneumonia in adults, but confirmation of the role of these viruses in pulmonary infections in adults awaits additional research.

Viruses play a part in adult pneumonia, but the exact role some viruses play in these infections awaits additional studies to determine whether they are innocent bystanders, organisms predisposing individuals to subsequent infections, or causative microorganisms.

Notes

Acknowledgments. The Infectious Diseases Society of America/American Thoracic Society guidelines for management of community-acquired pneumonia were published previously in *Clinical Infectious Diseases* [81]. We appreciate the editorial work of Veronica Hogue.

Potential conflicts of interest. T. C. C. is a board member of the Irvine Health Foundation and is on the speakers' bureau for the University of California, Irvine, and the Medical Education Speakers Network.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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