Viral Pneumonia in Adults

Ren-Guang Wu

Department of Internal Medicine, Chung-Kang Branch, Cheng-Ching General Hospital

Abstract

Molecular diagnostic tests have greatly increased our understanding of the role of viruses in pneumonia, and findings indicate that the incidence of viral pneumonia has been underestimated. The most commonly identified viruses in community-acquired pneumonia (CAP) are influenza, rhinovirus, respiratory syncytial virus (RSV), and human metapneumovirus (hMPV). Viral infections are common in adults with CAP, ranging from 10-30% of diagnosed cases. Polymicrobial infections involving bacterial and viral pathogens are frequent and may be associated with severe pneumonia. Besides, cytomegalovirus, herpes simplex and herpes zoster virus may cause severe respiratory illness and life-threatening pneumonia in immunocompromised adults (neoplasm, organ-transplantation, acquired immunodeficiency syndrome, AIDS). (J Intern Med Taiwan 2013; 24: 317-327)

Key Words: Viral pneumonia, Influenza virus, Parainfluenza virus, Rhinovirus, Coronavirus, Adenovirus, Cytomegalovirus, Herpes simplex virus, Varicella zoster virus, Human metapneumovirus, Hantavirus

Introduction

Viral pneumonia accounts for the large proportion of childhood pneumonia, which decreases in frequency in healthy young and middle-aged adults, but increases substantially among the elderly. Previous studies on etiology of community-acquired pediatric pneumonias often demonstrate viruses to be the second most common etiologic cause, ranging from 13-50% of diagnosed cases. Virus infections are common in adults with pneumonia, ranging from 15-29% of diagnosed cases. Easily transmissible viruses such as influenza, rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), are the most common.

Presence of viral epidemics in the community, speed of onset of illness, symptoms, biomarkers, radiographic changes, and response to treatment can help differentiate viral from bacterial pneumonia. However, no clinical algorithm exists that will distinguish definitively the cause of pneumonia. Depending on the virulence of the microorganism as well as the age and comorbidities of the patient, viral pneumonia can vary from a mild illness to a life-threatening disease in adults.

Bacteria continue to have a predominant role in adults with pneumonia. Polymicrobial infections involving bacterial and viral pathogens are frequent and may be associated with severe pneumonia.
Pathophysiology

After inhalation, most respiratory viruses tend to multiply in the epithelium of the upper airway and secondarily infect the lung via airway secretions. The mechanism of damage to pulmonary tissues depends on the virus involved. Some viruses are mainly cytopathic, directly affecting the pneumocytes or the bronchial epithelial cells, while others, overplentiful inflammation from the immune response accounts for the pathogenic process\(^5,6\).

Respiratory syncytial viruses damage the respiratory tract and stimulate the release of several factors, including histamine, leukotriene C4, and virus-specific immunoglobulin E. RSV infections can also alter bacterial colonization patterns, increase bacterial adherence to respiratory epithelium, reduce mucociliary clearance, and alter the phagocytosis response\(^6\).

Infection with the influenza virus impairs macrophage function, as well as NK cells-mediated TNF-\(\alpha\) expression and antibacterial host defense, leading to bacterial (especially staphylococcus) superinfection\(^7\).

Mucociliary clearance is impaired in viral respiratory tract infection, and bacterial adherence to respiratory epithelium occurs. Influenza-induced tissue damage is hypothesized to increase susceptibility to *Streptococcus pneumoniae* infection by increasing adherence to the respiratory epithelium\(^8\).

This impairment of local immune and respiratory defenses may explain why as many as 50% of outpatients with bacterial pneumonia have a concurrent viral infection.

Different proteases from various microorganisms in the respiratory tract are capable of enhancing influenza virus infectivity and pathogenicity by proteolytic activation of hemagglutinin\(^9\). *Staphylococcus aureus* could activate HA directly. A similar indirect effect on HA activation is induced by streptokinase and staphylokinase, which generates plasmin via plasminogen activation. It is proposed that plasminogen-activating streptococci and staphylococci facilitate viral replication and pathogenicity.

**Transmission Routes of Viral Pneumonia**

The mechanism of viral transmission of pneumonia varies with the type of virus. Transmission routes for selected viral pneumonias are summarized as Table 1\(^10\).

**Host Defense**

The host pulmonary defense is composed of the following four elements (Table 2)\(^11,12\).

**Viral Pneumonia in the Elderly**

Elderly persons are at increased risk of infection and complications. The delay in clearance of inflammatory process, multiple comorbidities,

<table>
<thead>
<tr>
<th>Table 1. Transmission routes of viral pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmission route</td>
</tr>
<tr>
<td>Inhalation of infected aerosol</td>
</tr>
<tr>
<td>Spread by healthcare personnel or hospital contact (nosocomial pneumonia)</td>
</tr>
<tr>
<td>Inhalation of infected excreta from diseased rodents</td>
</tr>
<tr>
<td>Transplantation of contaminated organs or blood products</td>
</tr>
<tr>
<td>Lower-respiratory aspiration of virus asymptotically shed in the saliva</td>
</tr>
<tr>
<td>Direct contact with contaminated lesions</td>
</tr>
</tbody>
</table>
waning cellular, humoral, and innate immune functioning may impair viral clearance\textsuperscript{13}, which allows spread of the virus to the lower respiratory tract resulting in pneumonitis. Elderly persons also have impaired cough reflex and protection of the respiratory tract due to comorbidities.

**Etiology and Clinical Features**

**Influenza Virus**

Influenza virus represents a common cause of pneumonia in the adult population, infection rates have been 10-20\% during outbreaks and as high as 50\% during epidemics. The highest rates of hospitalization for influenza occur in preschool-aged children and in the elderly population.

The influenza viruses, which belong to the *Orthomyxoviridae* family, are enveloped, single-stranded, RNA viruses, and are classified as serotypes A, B, and C.

Influenza type B causes illness that usually is seen in relatively closed populations such as military service or elementary schools. Influenza type C is less common and occurs as sporadic cases.

Influenza type A is usually the most virulent pathogen and the viruses caused pandemics in 1918 (H1N1), 1957 (H2N2), 1969 (H3N2), and 2009 (H1N1)\textsuperscript{14}. The influenza virus sustains its infectivity by undergoing antigenic drift (small number of amino acid substitutions) that alter epitopes targeted by neutralizing antibodies, and major antigen variation (shift), due to changes in the protein structure of the surface protein, hemagglutinin\textsuperscript{11}. Influenza type A can alter surface antigens and infect animals; this characteristic accounts for its ability to create a large reservoir for persistent infection between humans and animals. Epidemics occur when a viral drift occurs, and pandemics are seen with viral shift because most people have no prior immunity to the virus.

The H5N1 avian influenza seems to be more virulent than seasonal influenza, as a threat that could cause a severe pandemic. With a high mortality rate (59\%) in patients infected by high pathogenic avian influenza, the median time from disease onset to death was only 9 days\textsuperscript{15}. The clinical feature included pneumonia, acute respiratory distress syndrome (ARDS) or multiple organ failure.

More than 600 human HPAI H5N1 cases have been reported to WHO from 15 countries in Asia, Africa, the Pacific, Europe and the Near East since November 2003. Approximately 60\% of the cases are fatal. Indonesia, Vietnam and Egypt have reported the highest number of human HPAI H5N1 cases. The majority of HPAI H5N1 cases have occurred among children and young adults. Most cases of H5N1 have been linked to contact with infected poultry. Other HPAI H5N1 risk factors include visiting a live poultry market and prolonged, unprotected close contact with a sick HPAI H5N1 patient\textsuperscript{15}.

<table>
<thead>
<tr>
<th>Pulmonary host defense</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical barriers</td>
<td>Nostril hairs filter particles larger than 10 microns; Sharp-angle branching of the central airways helps the 5~10-micron particles impact in the mucosa. Mucociliary clearance facilitates the excretion.</td>
</tr>
<tr>
<td>Humoral immunity</td>
<td>*Mucosal immunoglobulin A (IgA), systemic IgG (vaccination or de novo); *Resident antigen-specific memory B cells.</td>
</tr>
<tr>
<td>Phagocytic cells</td>
<td>*Phagocytic cells consist of polymorphonuclear cells; alveolar and interstitial macrophages; *Respiratory dendritic cells –surveillance and modulation of active immune response or tolerance</td>
</tr>
<tr>
<td>Cell-mediated immunity</td>
<td>Cell-mediated immunity is the most important defense mechanism against the intracellular viral pathogens. CD8(^+) memory or effector T cells tend to dominate the lymphocyte component of the virus-induced inflammatory component.</td>
</tr>
</tbody>
</table>
There have been studies of the levels of cytokines in humans infected by the H5N1 influenza virus. Of particular concern is elevated levels of tumor necrosis factor-alpha, associated with tissue destruction and increased production of other cytokines. Infected with high pathogenic avian influenza may trigger intense inflammatory cascade, so called 'cytokine storm', and severe tissue damage, which ultimately result in death16.

The H1N1 (swine) influenza: Initially reported as an outbreak in Mexico and subsequently the United States, infection from a novel swine-origin influenza A (H1N1) rapidly spread to become a worldwide pandemic in 2009. With sustained human-to-human transmission in North America, WHO raised the global pandemic alert to phase 5 in a scale of 6, meaning a pandemic is imminent. As of June 9, there were 25,288 confirmed cases and 139 deaths worldwide with Mexico accounting for the 24.19% of the cases and 77.7% of the deaths17. Virus-associated hemophagocytic syndrome may play an important role in development of multiorgan failure and ensuing death in H1N1 infection18. WHO had declared that H1N1 in post-pandemic period in Aug. 2010, and expected the virus to take the behavior of seasonal influenza virus.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is the second most common viral cause of pneumonia in adults. RSV is highly contagious, spreading via droplet and fomite exposure. Most children are infected before the age of 5 year, the infection rate during an epidemic approaches 100% in certain settings such as kindergarten, but the resulting immunity is incomplete19. Reinfection in young adults is common but mild. However, the more severe lower respiratory tract infection and pneumonia increases with advancing age. In comparison with influenza, the RSV pneumonia is accompanied by more wheezing, sputum production and nasal congestion, and less constitutional symptoms, such as fever, myalgia and gastrointestinal upset. Seventy percent of patients with RSV pneumonia have a normal WBC count, compared with 40% of those with bacterial pneumonia. Eleven percent to 30% of RSV-infected patients may have evidence of mixed viral-bacterial infection13.

Two major antigenic groups of RSV (A and B) cause annual winter epidemics of respiratory disease. In a study of 1200 adults with CAP, RSV (4.4% of cases) was the third most commonly identified pathogen, compared with S. pneumoniae (6.2% of cases), influenza viruses A and B (5.4% of cases), and Mycoplasma pneumoniae (4.1%)20.

Chest radiographs typically show patchy bilateral alveolar infiltrates and interstitial changes and chest CT often reveals centrilobular nodules and bronchial wall thickening21.

In adults, RSV pneumonia is associated with a mortality rate ranging from 11 to 78%, depending on the severity of underlying immune suppression22. The revelation of RSV as a cause of death in the elderly is an important finding. However, adults are not often tested or treated for RSV with inhaled ribavirin. Given the new study results indicate that RSV accounts for the same burden of mortality as influenza virus in elderly people, RSV infections may present as community-acquired pneumonia or COPD exacerbations.

Adenoviruses

Adenoviruses cause a wide spectrum of clinical illnesses, including conjunctivitis, febrile upper respiratory disease, pneumonia, gastrointestinal illness, hemorrhagic cystitis, rash, and neurologic disease. Adenoviruses are extremely contagious. Types 4, 7 and 14 viruses are responsible for outbreaks of respiratory disease. Adenovirus serotype 14 (subgroup B) is a more virulent strain that has been reported to cause severe respiratory illness and pneumonia in immunocompetent adults23.
In 2007, adenovirus serotype 14 caused a large, sustained outbreak of febrile respiratory illness with substantial mortality and morbidity among military trainees in Texas and later in a residential care facility in Washington State\textsuperscript{24}. In a community outbreak of severe respiratory illness in Oregon, the clinical features included fever (84%), tachypnea (77%), hypoxia (48%), and hypotension (43%). Of the 24 chest x-rays obtained, 21 (88%) had abnormal findings, with lobar consolidation being the most common pattern. The median age of patients was 52 years, and 76% required hospitalization, 47% required critical care, 24% required vasopressors, and 18% died\textsuperscript{25}.

**Parainfluenza Virus**

Parainfluenza virus (PIV) is a common cause of seasonal upper respiratory tract infections in children and adults. PIV initially infects epithelial cells of the nose and oropharynx and then spreads distally to the lower respiratory tract. By adulthood, more than 90% of individuals have antibodies to PIV. With incomplete immunity, reinfection can occur. Among immunocompetent adults, PIV usually cause asymptomatic or mild, upper respiratory tract infections. However, PIVs can cause croup, bronchitis, pneumonia, and severe respiratory illness in adults or elderly, particularly debilitated nursing home residents. Studies indicate that PIV may play an important role in the etiology of respiratory tract infections in lung transplant recipients with an estimated incidence of 5.3 per 100 patients. PIV is also an important pathogen mimicking clinical presentation of H1N1 pneumonia\textsuperscript{26}.

**Rhinovirus**

Rhinoviruses, the most frequent cause of the common cold, can extend beyond the oropharynx and may cause infections in the lower respiratory tract, including pneumonia. Prominent nasal congestion, cough, and constitutional symptoms characterize the illnesses. Jennings et al showed a viral diagnosis was made in 88 (29%) of 304 patients with CAP, with rhinoviruses and influenza A being the most common\textsuperscript{2}. Two or more pathogens were detected in 49 (16%) patients, 45 of whom had mixed viral and bacterial infections. There were no reliable clinical predictors of viral pneumonia, although the presence of myalgia was associated with pneumonia caused by any respiratory virus (odds ratio [OR], 3.62) and influenza pneumonia (OR 190.72). Mixed rhinovirus/pneumococcal infection was associated with severe pneumonia.

Lung transplant recipients are particularly at risk of complications from rhinovirus, the most frequent respiratory virus circulating in the community. Rhinoviral infection can be persistent in lung transplant recipients with graft dysfunction\textsuperscript{27}, and the virus can be detected in the lung parenchyma.

**Human Metapneumovirus**

Human metapneumovirus (hMPV) is a relatively newly discovered respiratory pathogen and a significant cause of respiratory illness in children and adults. This virus is spread via droplet and fomite exposure. Most surveys indicate that by age 5 years, almost all children have been exposed to it. Without effective immunity, reinfection occurs frequently throughout life\textsuperscript{28}. Like influenza A and RSV, hMPV is also a major contributor to the burden of wintertime respiratory illnesses in older adults. Illnesses due to hMPV infection resulting in hospitalization and mortality have been frequently reported, and the presence of underlying cardiopulmonary disease and old age appear to be risk factors for severe illness.

In a study of 1386 adults hospitalized for acute cardiopulmonary disease and asthma, respiratory failure or congestive heart failure) during four consecutive winters in the United States, hMPV was identified in
8.5% (range, 4.4 to 13.2%) by reverse-transcriptase polymerase chain reaction and serologic testing.

Coronavirus

Coronaviruses are single-stranded RNA viruses, the surface being covered by crownlike projections, giving the virus its name. Transmission is by transfer of nasal secretions and aerosols caused by sneezing and coughing. It is second to rhinoviruses as a cause of the common cold and is very infrequently to cause severe lower respiratory tract infection. Coronaviruses have large RNA genomes and there are many deletion mutations and a very high frequency of recombination resulting in formation of new strains.

In late 2002, a new syndrome with moderate to severe respiratory illness and a relatively high mortality was observed in Guangdong Province of southern China. It was later named severe adult respiratory syndrome (SARS). SARS was caused by a novel coronavirus (CoV) that crossed the species barrier through close contacts and infected humans and animals. Initial clinical symptoms are usually mild, but after a few days (typically 5~7 days), the patient may develop a progressive shortness of breath and hypoxemia. Respiratory distress leads to death in up to 30% of case. The initial outbreak of SARS peaked in April 2003. By that time, there had been about 8,000 cases worldwide and 775 deaths.

WHO announced that the last chain of human transmission of SARS coronavirus (SARS-CoV) was broken on 5 July 2003, and thus the epidemic was over. However, the virus re-emerged from one of several sources: from an animal source, from a laboratory accident, or from undetected transmission cycles in human populations. With rapid detection and management, none of these cases has been fatal nor resulted in secondary transmission.

The chest radiograph usually reveals a peripheral opacity, with lower zone dominance. The infiltrates ranges from ground-glass to consolidation in appearance. In the advanced cases, there is widespread opacification which may be coalescent to large consolidative areas. Cavitation, pleural effusion or lymphadenopathy are not typical features of this disease.

Varicella-zoster Virus

Varicella-zoster virus (VZV) is a highly contagious herpes virus that is spread by the respiratory route or direct contact with active skin lesions. The virus remains quiescent but reactivates sporadically and infrequently to cause herpes zoster. The molecular mechanisms that maintain VZV latency are not fully understood but reactivation of the virus is clearly related to declining VZV-specific cell-mediated immunity (CMI). CMI to VZV declines markedly in immunocompromised patients and in the elderly.

Varicella pneumonia complicates approximately 2-10% of the cases of VZV infection in adults, and the leading cause of death among vaccine-preventable diseases. Complications include secondary bacterial pneumonia, acute respiratory failure, encephalitis, and hepatitis. The estimated mortality of VZV pneumonia may reach 25% in past years and declined steadily from 19% in 1960-1970 to 6% in 1991-2000. In a recent, 10-year retrospective study of 46 cases revealed that the most common symptoms were: skin blisters (100%), fever (83%), cough (83%), dyspnea (63%), and pleuritic chest pain (70%). Once diagnosed, 98% were treated with acyclovir, combined with steroids in 6 and with antibiotics in 3 complicated with bacterial pneumonia. Eight patients had a significant hypoxemia and required mechanical ventilation. Despite the severity of disease, no patient died who received early antiviral therapy.
Cytomegalovirus

Cytomegalovirus (CMV) is a common cause of asymptomatic infections. The transmission is primarily through body fluid contact, including milk, semen, and blood products. The prevalence of antibodies to CMV in adults ranges from 40 to 100%, and reactivation of latent infection is almost universal in immunosuppressed hosts, including transplant recipients and individuals infected with the human immunodeficiency virus. In cancer patients receiving allogeneic bone marrow transplants, CMV pneumonia has a prevalence of 15% and a mortality rate of 85% if left untreated. Acute graft-versus-host disease is the major risk factor for CMV pneumonia in these patients.

Herpes Simplex Virus

Herpes simplex virus (HSV) is spread by contact with active lesions. Pneumonia may develop from primary infection or reactivation. HSV can cause pneumonia in immunocompromised hosts, with a mortality rate up to 80%. Pathologically, HSV infection can have three main forms of pulmonary involvement: necrotizing tracheobronchitis, necrotizing pneumonia and interstitial pneumonitis. Focal HSV pneumonia appears to result from contiguous spread of the tracheobronchial tree to lung parenchyma, whereas diffuse interstitial pneumonia appears to be a manifestation of hematogenous dissemination of the virus.

The rate of HSV pneumonia can be as high as 70-80% in early HSCT recipients not receiving prophylaxis, and it can be decreased to 5% with acyclovir prophylaxis. HSV pneumonia may be acquired in organ transplants by endogenous reactivation caused by immunosuppression or may be introduced from colonized oropharyngeal secretions into the lower respiratory tract during intubation in patients on ventilators. In ventilated patients without severe preexisting lung disease, HSV pneumonia presents with otherwise unexplained profound/prolonged hypoxemia or “failure to wean.”

Hantavirus

Hantaviruses are the etiologic agents of two zoonotic diseases: hemorrhagic fever with renal syndrome (HFRS) and hantavirus cardiopulmonary syndrome (HCPS). The hantavirus is transmitted by arthropod vectors, and it is harbored by rodents. Rodents, which are chronically infected, excrete hantaviruses from urine, saliva, and feces. Infection occurs after aerosols of infectious excreta are inhaled.

In HFRS, the severity of the disease varies depending on the particular virus involved. Hantaan (HTNV) and Dobrava viruses (DOBV) tend to produce the more severe disease, with mortality rates of 5-10%. Seoul virus (SEOV) typically produces disease of intermediate severity with a mortality rate of 1%. Clinically, HFRS presents with sudden onset of fever, chills, headache and myalgia with renal impairment. Clinical features also include thrombocytopenia and hemorrhages as a result of the vascular endothelium dysfunction.

It has been suggested that HFRS pathogenesis is likely to be a complex multifactorial process that includes contributions from immune responses, platelet dysfunction, dysregulation of endothelial cell barrier functions and hosts' genetic factors. Increased immune cytokines, such as IL-1, IL-6, IL-10 and TNF-α, were suggested to be involved in the pathogenesis in patients with HFRS.

Infection with hantavirus can progress to hantavirus pulmonary syndrome (HPS), caused by Sin Nombre hantavirus, first recognized in 1993 in the US. Cases of HPS continue to be reported in the United States. As of July 2010, 545 cases of HPS had been reported in the United States from 32 states. The mortality rate for HPS is 35%.
Diagnostic Considerations

Over the past decade, new developments in diagnostic techniques have led to a significant improvement in the ability to detect viruses in the respiratory tract. Viral diagnostic methods include culture, rapid antigen detection, RT-PCR, and serologic testing. Respiratory secretions appropriate for testing include nasal swab, sputum, tracheal aspirates, and bronchoalveolar lavage specimens.

**Rapid antigen testing** is commercially available for influenza viruses A and B and RSV, and can offer immediate results. Rapid antigen detection tests provide faster results because the test is performed directly on specimens obtained from nasal or nasopharyngeal swabs. Sensitivity for seasonal influenza in adults ranges between 50% and 60%, and specificity is greater than 90%. The sensitivity with rapid tests is significantly lower (51-63%) when compared with RT-PCR. Rapid influenza tests unfortunately have very poor sensitivity and specificity for the avian H5N1 influenza virus and are therefore not recommended. Many institutions screen patients with rapid tests and perform culture only if rapid testing is negative. Rapid RSV antigen tests are useful in young children who shed high titers of virus, but results are disappointing in adults with low viral shedding. RT-PCR is relatively sensitive and specific for the diagnosis of the common respiratory viruses. Although rapid, these assays are expensive and not widely available outside of major medical centers. However, a newly developed technique, multiplex reverse transcriptase polymerase chain reaction (MRT-PCR, Hexplex; Prodes), permits rapid detection of influenza virus types A and B, RSV (types A and B), adenoviruses, PIV (types 1, 2, and 3), hMPV, and rhinovirus in appropriate respiratory tract secretions.

**Serology**: With high frequency of past infection in adults, the presence of preexisting antibody precludes a single serologic test to detect IgG antibody. IgM assays have generally not been useful. Serologic testing provides retrospective diagnosis

---

**Table 3. Diagnostic techniques used for viral pneumonia**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Viral Culture</th>
<th>Cytologic Evaluation</th>
<th>Rapid Antigen Detection</th>
<th>Gene Amplification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus</td>
<td>HA*, SV†</td>
<td>Intranuclear inclusions</td>
<td>IF‡, ELISA§, RT-PCR#</td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>CE, SV</td>
<td></td>
<td>IF, ELISA</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Paramyxoviruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>CE, SV</td>
<td>Eosinophilic cytoplasmic inclusions</td>
<td>IF, ELISA</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>HA, SV</td>
<td>Eosinophilic intranuclear inclusions</td>
<td>IF, ELISA</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Measles virus</td>
<td>HA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Herpes simplex</em> virus</td>
<td>CE, SV</td>
<td>Cytoplasmic inclusions</td>
<td>IF, ELISA</td>
<td>PCR</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>CE</td>
<td>Cytoplasmic inclusions</td>
<td>IF</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>CE, SV</td>
<td>“Owl’s eye” cells</td>
<td>IF, ELISA</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Hantavirus</td>
<td></td>
<td>Antibodies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Viral antigen in tissue by IHC*</td>
<td></td>
<td>Viral RNA in blood or tissue.</td>
</tr>
</tbody>
</table>

* HA - Hemaglutination.
† SV - Shell viral culture.
‡ IF - Immunofluorescence. *IHC: immunohistochemical staining.
§ ELISA - Enzyme-linked immunosorbent assay.
* CE - Cytopathogenic effects.
* RT-PCR - Reverse transcriptase polymerase chain reaction.
when a 4-fold increase in a specific antibody is detected by complement fixation or EIA.

Cytologic Evaluation: Respiratory secretions, bronchoalveolar lavages, and tissue specimens can be examined using cytologic techniques. Intranuclear inclusions often exist in cells infected with DNA viruses; cytoplasmic inclusions usually are present in cells infected with RNA viruses. The presence of viral inclusions is diagnostic for viral infection but not specific for certain virus.

**Viral culture** remains the gold standard for diagnosis, but optimal results require prompt transportation of the specimen on ice for immediate inoculation. The use of an appropriate viral transport medium is required; this consists of enriched broth containing antibiotics and a protein substrate. Specimen from nasopharyngeal swab, sputum, tracheal aspirates, bronchoalveolar lavage, biopsy from lower respiratory tract, may be submitted for viral culture.

Viral cultures are usually performed on special cell lines (eg, monkey kidney cells, diploid fibroblasts). The cell cultures are incubated at 35°C and are examined microscopically for an incubation of 2-20 days when cytopathic effects appear and include eosinophilic and diffuse basophilic intranuclear inclusions. Serotype 14 can be also diagnosed by direct fluorescent antibody rapid antigen detection, and PCR.

### Table 4. Diagnostic techniques used for respiratory virus

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Viral culture</th>
<th>Rapid antigen detection</th>
<th>RT-PCR</th>
<th>Histology</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza virus</td>
<td>from nasal/throat swabs, nasal washes, and sputa. Ninety percent of positive cultures can be detected within 3 days.</td>
<td></td>
<td>Many rapid tests exist for influenza virus types A and B, but sensitivities are 40-80% when compared with viral culture; however, the specificity is high (85-100%).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV</td>
<td>RSV can be isolated via culture, the nasopharyngeal washes or tracheal secretions are of higher yield than nasal swabs. About 15% of nasopharyngeal wash specimens are positive, compared with 71% of endotracheal secretions and 89% of bronchoalveolar washes.</td>
<td>Rapid detection by EIA has a sensitivity of 50-90% (higher in children but lower in adults), but specificity is high (90-95%).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>isolated from respiratory secretions. Cytopathic effects appear in 2-20 days and include eosinophilic and diffuse basophilic intranuclear inclusions.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIV</td>
<td>from nasal secretions. Isolation of this virus is strong evidence of its infection.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hMPV</td>
<td>RT-PCR is the preferred method for diagnosis.</td>
<td></td>
<td>Viral culture: cultures need to be observed for 21 days for cytopathic effect.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>Histopathologic findings (owl’s eyes basophilic intranuclear inclusions) on lung biopsy tissue.</td>
<td>Blood CMV PCR and/or CMV blood culture positivity lends further support for the diagnosis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella-zoster virus (VZV) infection and pneumonia can be diagnosed mostly on clinical grounds.</td>
<td>Viral culture: VZV can be isolated from vesicular fluid, respiratory secretions, or cerebrospinal fluid (CSF) by culture.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSV</td>
<td>lower respiratory tract secretions (preferably bronchoscopy specimen)</td>
<td>Histology of pulmonary tissue shows multinucleated giant cells.</td>
<td></td>
<td>*Antigen detection and PCR of sputa are overly sensitive (false positives). *Serologies are not useful for diagnosis of pneumonia.</td>
<td></td>
</tr>
<tr>
<td>Hantavirus</td>
<td>Serology: detection of hantavirus–specific antibody</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
period of 14 days. The cultures are examined for cytopathogenic effects and for evidence of viral growth. The cytopathogenic effect is the formation of syncytial collections of multinucleated giant cells and rarely is virus specific. Further identification of viruses is accomplished using immunofluorescence methods or nucleic acid probes.

Conclusions

Molecular diagnostic tests have greatly increased our understanding of the role of viruses in pneumonia, and findings indicate that the incidence of viral pneumonia has been underestimated. Rapid antigen testing is commercially available for influenza viruses A and B and RSV. RT-PCR is relatively sensitive and specific for the diagnosis of the common respiratory viruses. A newly developed technique, multiplex reverse transcriptase polymerase chain reaction (MRT-PCR), permits rapid detection of influenza virus types A and B, RSV, adenoviruses, PIV, hMPV, and rhinovirus in appropriate respiratory tract secretions.

References

由於分子生物學技術的進展，近年來病毒性肺炎診斷率明顯提高，其中以流行性感冒病毒為常見，其他為副流感病毒、呼吸道合胞病毒、鼻病毒、人類間質肺炎病毒、冠狀病毒、巨細胞病毒、腺病毒、單純皰疹、水痘-帶狀皰疹等病毒。病毒性肺炎多發生於冬春季節，可散發流行或暴發大流行。在社區肺炎中，病毒感染約占10%~30%，患者多為老年人或免疫不全的病患。病毒性肺炎為飛沫傳染、吸入傳染或接觸傳染，常因上呼吸道病毒感染向下蔓延所致，常伴氣管-支氣管炎。病毒也常伴隨細菌或其他非典型病原菌的感染，加劇肺炎的嚴重程度。近年來由於免疫抑制藥物廣泛應用於腫瘤、器官移植，以及愛滋病的發病人數逐年增多，巨細胞病毒、單純皰疹病毒、水痘-帶狀皰疹病毒等，都可引起嚴重且致命的肺炎。