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28 VIRAL PNEUMONIA

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Viral pneumonia is one of the most common maladies affecting infants and children throughout the world. Acute respiratory infection continues to be a leading cause of mortality in young children.[1] Of the estimated 8.795 million worldwide deaths in children younger than 5 years of age in 2008, infectious diseases caused 68% (5.970 million), with pneumonia causing the largest percentage (18%; 1.575 million; uncertainty range 1.046 million to 1.874 million).[1] About 40% of these cases are caused by viral infections. Pneumonia, a respiratory disease characterized by inflammation of the lung parenchyma, is usually caused by viruses, bacteria, or irritants. The term *pneumonia* refers to infection of the lung parenchyma and excludes the tissues of the airway such as the bronchi. However, it is thought that acute viral lower respiratory tract infections (LRTIs) in children affect all of the epithelial cells lining the airway, from the nasopharynx to the alveolar bed. Therefore, viral pneumonia is often a component of a more generalized respiratory tract infection syndrome.

INCIDENCE

It is well established that children younger than 5 years of age, especially infants, have a high burden of disease and hospitalization from respiratory syncytial virus (RSV), metapneumovirus influenza virus (MPV), and parainfluenza viruses (PIVs). However, studies conducted during the last several decades have struggled to define precise quantitative models for the incidence of these diseases. Most large studies were conducted in hospitals and thus lacked a known denominator of subjects at risk. These studies also varied by differences in geographic location of the study, type of hospital, age of the patients, season, criteria for admission, severity of disease, and number and type of diagnostic tests performed. The relatively new use of molecular diagnostic tests has increased our ability to diagnose virus infection, but comparison of data from these studies with data from cell culture–based studies is problematic.

Prospective, active population-based surveillance is needed to define incidence. The U.S. Centers for Disease Control and Prevention sponsored studies in young children who were hospitalized for acute respiratory illness from October 1, 2000, to September 30, 2001, in Monroe County, New York (Rochester area), and Davidson County, Tennessee (Nashville area).[2] Eligible children younger than 5 years of age were those who resided in surveillance counties and were hospitalized for febrile or acute respiratory illness. Viral culture and polymerase chain reaction identification of viruses from nasal and throat samples were obtained from all surveillance children, providing population-based rates of hospitalization for RSV, influenza virus, and PIV, as well as demographic, clinical, and risk factor assessment for each virus. Of the 592 enrolled children, RSV was identified in 20%, influenza in 3%, PIV in 7%, other respiratory viruses in 36%, and no detectable virus in 39%. Population-based rates of acute respiratory illness hospitalizations in children younger than 5 years of age were 18 per 1000. Virus-positive hospitalization rates per 1000 children were 3.5 for RSV, 1.2 for PIV, and 0.6 for influenza virus. Younger age (particularly younger than 1 year of age), African-American and Hispanic race/ethnicity, male gender, and presence of chronic underlying illness were associated with higher hospitalization rates.

ETIOLOGIC AGENTS

The etiologic agents that cause viral pneumonia are well defined. The cause of viral pneumonia varies depending on the age of the child, the setting in which the virus was acquired, the season, and the presence of medical or environmental risk factors. Although a very long list of viruses has been reported to cause pneumonia, the astute clinician can narrow the cause to a short list of potential agents using a careful medical history and physical examination. Common causes of viral pneumonia are shown in Box 28-1.

NEONATAL PNEUMONIA

Perinatal/Transplacental Acquisition

Bacteria, viruses, and noninfectious conditions (e.g., meconium aspiration) can cause pneumonitis at the time of birth. Viruses are infrequently the cause of this presentation, and pneumonia often is only part of a more generalized presentation of a systemic disease. Rubella and cytomegalovirus (CMV) infection associated with systemic disease in the mother can be associated with severe congenital or neonatal disease that probably is acquired by the transplacental route, presumably through the hematogenous spread of virus. Pneumonia manifests with signs of respiratory distress (e.g., retractions, grunting, tachypnea, and cyanosis) that sometimes requires immediate resuscitation and mechanical ventilation because of depressed respiration. Neonatal viral pneumonia can present with more nonspecific systemic signs of illness, such as apnea, bradycardia, poor peripheral perfusion, or temperature instability. These signs also are found frequently in bacterial pneumonia in the neonatal period. Usually, infants with congenital CMV or rubella pneumonia exhibit additional signs of congenital infection, such as petechiae, hepatosplenomegaly, and low birth weight. CMV infection is detected by testing the infant's urine in shell vial or conventional cell culture.

BOX 28-1 Etiologic Agents of Acute Acquired Viral Pneumonia in Children, by Age

Perinatal
CMV
HSV types 1 and 2
Enteroviruses
Rubella

3 Weeks to 3 Months
RSV subgroups A and B
hMPV subgroups A and B
PIV type 3

4 Months to 4 Years
RSV subgroups A and B
hMPV subgroups A and B
PIV types 1, 2, and 3
Influenza A and B
Rhinoviruses
Adenoviruses

Older Children and Adults
Influenza A and B
Military recruits: Adenovirus types 4 and 7

Viruses That Are Less Common or That Cause Pneumonia in Certain Settings
Adenovirus types 1, 2, 3, and 5
Enterovirus spp.: echovirus, coxsackievirus
Coronaviruses, SARS-coronavirus
Epstein-Barr, CMV, human herpesvirus 6 (in the immunocompromised)
Varicella-zoster
Developing world: measles, mumps
Endemic areas: Hantavirus

TRANSMISSION FROM THE BIRTH CANAL

Herpes simplex virus (HSV) type I or II infection of the mother's cervix can lead to exposure of the infant during labor or birth by the mucosal route, including aspiration. HSV is capable of infecting the infant via an ascending route from the vagina; the risk of transmission from an infected mother is increased after prolonged rupture of the membranes during labor. The infection may be acquired without prolonged rupture of the membranes during the passage through the birth canal. Transmission is more efficient if the mother is suffering a primary infection, as opposed to a re-activation. The presence of visible herpetic lesions is not needed for transmission to the infant. Herpes simplex virus infection commonly presents in the second week of life. The medical history from the families of infants with pneumonia at this age should consider risk factors, and the physical examination should seek other manifestations of herpetic infection. The cytopathic effects of HSV have been observed in the lungs of infants with pneumonia caused by herpes infection. Systemic HSV infection should be treated with a prolonged course of intravenous acyclovir. Enteroviruses commonly cause symptomatic or asymptomatic infections of the gastrointestinal tract during the summer and fall months. Infected mothers can transmit an enterovirus infection to the infant during birth, and these infections can cause severe systemic disease including pneumonia. When viral infection is acquired from contaminated amniotic fluid or in the birth canal, the infant may not be affected clinically in the first hours or days after birth.

TRANSMISSION IN THE NURSERY

Nosocomial transmission of viruses in the early postpartum period occurs, with surprising efficiency in some cases. The most common cause of nosocomial pneumonia is RSV, which occasionally causes nursery outbreaks.[3] Such outbreaks can be especially devastating in a neonatal intensive care unit if premature infants who require mechanical ventilation become infected. In this setting, infection is usually transmitted by fomites or directly from infected personnel via nasopharyngeal secretions.

INFECTION IN THE FIRST WEEKS OF LIFE

The most common causes of pneumonia in the developed world in the first weeks of life are RNA respiratory viruses, especially RSV. RSV causes yearly winter epidemics in the community that result in the hospitalization of between 0.5% and 4% of infants, depending on the population. During the winter months, RSV is often the major cause of hospitalization of infants, and entire infant wards in many children's hospitals have been dedicated for cohorting of infants during the annual epidemics. Nosocomial spread of virus during the epidemics is common, but it can be minimized by strict attention to contact isolation and hand hygiene.

VIRAL PNEUMONIA DURING EARLY CHILDHOOD

A large panel of respiratory viruses is capable of causing pneumonia during childhood. RSV; human metapneumovirus (hMPV); PIV types 1, 2, and 3; influenza virus types A and B; and adenoviruses make up the majority of cases. RSV is still the most frequent cause of severe respiratory infections in infants after the first weeks of life and in young children, and it is responsible for 75,000 to 125,000 hospitalizations each year in the United States.[4,5] The role of rhinoviruses in causing LRTI such as pneumonia is under much discussion. Rhinovirus infection in children is so common that evidence for rhinovirus infection can be found frequently in children without symptoms of disease. Therefore, attributing causality to rhinovirus in cases of pneumonia is more difficult than with other viruses. Nevertheless, rhinovirus is present significantly more often in cases of childhood pneumonia, and some experts believe that rhinovirus is the most common etiology of all types of LRTI in children. Human rhinoviruses, members of the family *Picornaviridae,* were first isolated in the 1950s, and now there have been over 100 serotypes identified based on nucleotide sequence homologies. Human rhinoviruses were divided into two major genetic groups in the past: designated HRV-A and HRV-B. More recently, a new rhinovirus group, HRV-C, has been found in some patients with LRTI. PIVs, commonly associated with laryngotracheitis (croup syndrome), also cause pneumonia but in less discrete epidemics than those caused by RSV. PIV infections are common in the fall months but can occur at any time of the year. Influenza A and B viruses cause sharp winter epidemics.

In the developing world, measles virus is still a major cause of pneumonia, especially in the setting of malnutrition or vitamin A deficiency, and mumps virus can cause LRTI. Influenza virus type C and PIV type 4 cause upper respiratory tract disease, but their ability to cause lower respiratory tract disease is less clear. Severe acute respiratory syndrome (SARS) was caused by SARS-coronavirus, which was first recognized in Hong Kong during a 2003 epidemic, and this disease affected children.[6] Morbidity was high following SARS, with approximately one fourth of patients requiring intensive care and/or mechanical ventilation support. SARS morbidity and mortality are milder in children than they are in adults, and pneumonia was only one of the disease manifestations of what appears to be a systemic illness. Other more conventional human coronaviruses also cause some cases of pneumonia (e.g., the long-recognized OC43 and 229E strains or the more recently identified coronavirus NL63 and HKU1 strains).[7] Varicella-zoster virus can cause pneumonia during primary infection, especially in older subjects. Other viruses cause pneumonia less commonly (e.g., Epstein-Barr virus, CMV, and human herpesvirus).[6] The immunocompromised are a special population at elevated risk for these infections, especially for CMV. Human bocavirus is a parvovirus that has been found in many respiratory secretions, but often in the same frequency in cases as in controls. Therefore, it is not clear that this agent is a significant cause of human disease.

The major features of the epidemiology of respiratory virus pneumonia caused by common agents was determined in the United States in detail mostly during the 1960s through the 1980s in a series of seminal longitudinal studies, such as the D.C. Children's Hospital studies,[8–11] Chapel Hill Pediatrics surveillance study,[12] the Vanderbilt Vaccine clinic surveillance studies,[13,14] the Tecumseh study of respiratory illness (Tecumseh, Michigan), and the Tucson Children's Respiratory Study. The principal viruses identified in association with pneumonia in otherwise healthy infants and children were RSV, PIV, and influenza viruses. These studies used cell culture–based or serologic detection for the most part, and it is fair to say that most of these studies did not have optimal culture systems for rhinoviruses or coronaviruses. More recently, very large studies using database methods, such as the U.S. National Hospital Discharge Survey data system[15,16] or the Tennessee Medicaid Database[17] (approximately 1% of U.S. children) have confirmed the earlier findings with larger numbers and added detail about the risk factors for severe disease. In the last several years, new data have emerged on the role of a newly identified paramyxovirus, hMPV,[18] which was shown to be one of the most common causes associated with LRTI in children.[19] Before 2001, studies could not address the epidemiology of this virus because it had not been discovered.

RISK FACTORS FOR PNEUMONIA

Most children are infected with the common respiratory viruses during the first years of life, but a minority suffers from lower respiratory tract disease or pneumonia to such an extent that it brings them to medical care. Studies have identified a number of risk factors for severe disease, especially young age, prematurity, preexisting lung disease (especially bronchopulmonary dysplasia), congenital heart disease, environmental exposure (smoking or wood fire heating), daycare, large number of siblings, low socioeconomic status, or birth near the start of the RSV season.[17] Exposures to infected children in the home or nosocomial exposure are pertinent historical risk factors.

PATHOGENESIS

Viral pneumonia is an infection of the cells surrounding the alveolar space. Alveolar walls thicken, and the alveolar space becomes occluded with exudates, sloughed cells, and activated macrophages. The clinical disease is distinguished by poor air exchange, first noted by poor oxygenation (detected by pulse oximetry or blood gas measurement) followed by CO_2 retention. The physiology of the disease reflects an inflammatory process that interferes with gas exchange, resulting in elevation of the alveolar-arterial Po_2 difference. Many cases of viral pneumonia in young children are also accompanied by inflammation of the bronchioles, and air trapping contributes to the poor level of gas exchange. Children compensate for respiratory compromise better than do adults, generally by increasing the respiratory rate. Children show a remarkable resilience when faced with respiratory compromise, even though their airways exhibit a much higher intrinsic level of resistance. Unrelieved tachypnea, however, can lead to exhaustion and respiratory failure. The histopathologic mechanisms underlying acute viral pulmonary disease in otherwise healthy children are not completely understood because lung tissue is rarely obtained for histology before mechanical ventilation or other medical interventions in previously healthy patients.

LIFE CYCLE OF THE VIRUSES *IN VIVO*

Despite significant advances in our understanding of the basic virology and molecular biology of these respiratory viruses based on *in vitro* studies, relatively little is known about the life cycle and spread of these viruses to the lung parenchyma *in vivo*. It is thought that the initial infection occurs in the nasopharynx after inoculation with contaminated respiratory secretions (fomite transmission) or exposure to large-particle aerosols containing virus. The viruses that cause pneumonia all have surface fusion proteins that mediate both virus-cell fusion and cell-cell fusion in monolayer cell culture. The viruses cause cytopathic effects following infection by inducing necrosis or apoptosis of infected cells. The viral fusion peptides of these viruses cause multinucleated cell (syncytium) formation in cell monolayer cultures. It is presumed that they cause syncytia formation *in vivo,* but the direct evidence for this is scarce. In fact, viruses that cause syncytium in nonpolarized cultured cells (i.e., cells that do not form tight junctions and segregate apical and basolateral cell membrane regions) often do not cause syncytia in polarized cell lines or primary cells in culture. Most of these viruses appear to infect both ciliated and nonciliated

cells in culture. Impaired mucociliary clearance caused by infection of ciliated cells probably contributes to progression to pneumonia. Whether these viruses infect type I or II pneumocytes more efficiently is not known. Some of the respiratory viruses cause an abortive round of infection in cultured macrophages or dendritic cells. Infection of these antigen-presenting cell types may contribute to inflammatory disease of the lung.

The mechanism for spread of infection to the lower respiratory tract within days of inoculation is unknown. Virus probably spreads by microaspiration of infected secretions or by cell-to-cell spread. The rapid time course of spread *in vivo* suggests that aspiration of infected secretions results in direct inoculation of the lower respiratory tract. Autopsy of fatal RSV cases has demonstrated the presence of relatively little virus antigen, and pathologic changes in fatal cases can be patchy in distribution. Bronchoalveolar lavage and tissue specimens from hematopoietic stem cell transplant patients or autopsies evaluated by direct immunofluorescence or immunoperoxidase stains revealed epithelial cells and macrophages that stain positive for RSV proteins, and electron microscopy revealed occasional epithelial cells with cytoplasmic inclusions composed of filamentous virions. There are limited autopsy data from PIV-infected or influenza-infected humans. In summary, the population(s) of cells that are the primary target of respiratory virus infections in humans are probably epithelial in origin but have not been fully defined in normal hosts.

VIRUS RECEPTORS ON HOST CELLS

The hemagglutinin protein of influenza virus mediates virus attachment to a ciliated cell glycoconjugate terminating in sialic acid and causes fusion with an intracellular endosomal membrane at low pH. The PIV hemagglutinin-neuraminidase glycoprotein mediates attachment to sialic acid–containing host cell receptors. The RSV surface protein that mediates attachment is the RSV G (glycosylated) glycoprotein. Its cellular receptor is not fully understood, but this glycosylated protein binds to heparan sulfates and to the CX3CR1 protein (the specific receptor for the CX3C chemokine fractalkine) through a CX3C motif in the viral protein.[20] The viability of mutant RSV strains lacking the viral G protein indicates that this attachment protein is not strictly required for replication in cell culture or in rodents. The RSV F protein binds to toll-like receptor 4[21] and to heparan sulfates and interacts with the cellular protein RhoA[22] nucleolin[22a] but whether any of these serves as a principal protein receptor is not clear. An association between common toll-like receptor 4 genetic polymorphisms and severity of RSV disease has been reported.

INFLAMMATION

The magnitude and character of the inflammatory response in the airway appear to be highly regulated by epithelial cell–derived cytokines and chemokines that attract and activate specific subsets of leukocytes associated with airway inflammation. Cytokine secretion appears to be highly regulated by nuclear factor κB (NF-κB) transcription factors, which are dimers of structurally related proteins retained in the cytoplasm by association with the inhibitory κB proteins. Upon various cellular stimulations usually related to stress or pathogens, the inhibitors are degraded and the nuclear factors κB translocate to the nucleus, where they bind to κB DNA elements to induce transcription of a large number of genes, especially those associated with immune responses. Nuclear factor interleukin 6 (NF-IL-6) regulates expression of cytokine and adhesion molecule genes without increased transcription. RSV infection induces increased expression of several cytokines, including IL-6 and IL-8, which are transcriptionally regulated by NF-κB and NF-IL-6. These cytokine-regulated pathways appear to contribute to airway inflammation during pneumonia.

Immune cells also probably play a major role in the pathogenesis of disease. Infected epithelial cells appear to initiate a cascade of events that represent components of the innate immune response. When infected epithelial cells secrete IL-6 and IL-8 and other soluble factors, they recruit and initiate activation of immune effectors. The chemokine RANTES (regulated upon activation, normal T cell expressed and secreted) is a chemoattractant for eosinophils, monocytes, T cells, and basophils that is secreted in response to infection with viruses such as RSV. Eventually, adaptive immune effectors such as $CD8^+$ T cells attack the virus-infected cells to eliminate the infection. This immune cytolysis is important to disease resolution but comes at the price of inducing some level of immunopathology. The cell surface factors that facilitate homing of lymphocytes to lung tissue are under investigation.

CLINICAL DISEASE

The clinical presentation of viral pneumonia includes increased respiratory rate and supracostal, intercostal, or subcostal retractions. Infants show nasal flaring, grunting, and marked retractions during severe disease. Vital signs reveal fever in about half of cases at presentation; fever higher than 103° F is much less common than in bacterial pneumonia but can occur. Systemic toxicity is less common than with bacterial infection because respiratory viruses (other than measles virus) rarely cause viremia. In fact, most respiratory viruses appear to be limited to the most superficial cells at the lumenal surface of the airway. Of the conventional respiratory viruses, influenza virus is the one that most frequently causes high fever and toxic appearance. Respiratory failure, heralded by a change in alertness due to hypoxia and CO_2 retention or decreased respiratory effort due to exhaustion, requires immediate action. Physical examination reveals crackles on auscultation, generally more prominent on inspiration. RSV disease in infants is commonly a mixed presentation of bronchiolitis and pneumonia, in which case expiratory wheezing is present in addition to inspiratory crackles. The viruses that cause pneumonia also cause upper respiratory tract infection. Therefore, concomitant coryza is common, complicated in about one third of cases with otitis media. Nasal obstruction caused by purulent nasal secretions contributes to the respiratory distress, especially in infants. Mild to moderate dehydration is common as a result of increased respiratory and other insensible losses, and poor oral fluid intake.

CLINICAL DIAGNOSIS OF PNEUMONIA

The terms *pneumonia* and *lower respiratory tract illness* have clinical, anatomic, and histologic definitions. *Lower respiratory tract illness* is defined clinically as the presence of crackles, rhonchi, or wheezes on physical examination or as infiltrates on a chest radiograph. Anatomically it is usually considered disease below the vocal cords. Pneumonia is an inflammation caused by infection of the lung parenchyma, comprising alveoli and interstitial tissue with possible extension to the bronchioles. Viral pneumonia during childhood is often one component of a lower respiratory illness that also affects the small and large conducting airways. For example, the most common presentation of severe RSV infection of infants is bronchiolitis and pneumonia.

RADIOGRAPHIC FINDINGS

Chest radiographs using the posteroanterior view are the principal diagnostic radiologic test for pneumonias. Children who have an effusion or an empyema identified on chest radiograph may need a computed tomography scan to define further the scope of the problem, but these complications are rare in viral pneumonia. Radiologic findings on chest radiographs of viral pneumonia are similar to those of bronchiolitis and reactive airways disease. The usual findings on chest radiographs are hyperaeration, prominent lung markings caused by bronchial wall thickening, and focal areas of atelectasis (Fig. 28-1). The hili may be somewhat prominent, but major hilar adenopathy is uncommon. The findings are commonly thought to differ from the typical case of bacterial pneumonia, which usually has been thought to present as lobar consolidation. It is true that most children with focal alveolar pneumonia have laboratory evidence of a bacterial infection, especially those with lobar infiltrates. However, half of the children with solely interstitial infiltrates on chest radiograph had evidence of bacterial infection in some studies.[23] Therefore, radiologic presentation of interstitial infiltrates alone does not distinguish between bacterial and viral pneumonia. One also cannot differentiate viral pneumonia from bronchiolitis or reactive airways disease on the basis of radiologic findings alone. Differentiation is based on non-radiologic factors such as the age of the patient and the clinical history. The chest radiograph in newborns with viral pneumonia usually shows bilateral diffuse densities or may have a granular appearance, similar to that found in hyaline membrane disease. When infection is congenital, radiographic changes may be present at birth, whereas the radiographs of infants infected during birth may be normal initially but can progress rapidly during the first days of life.

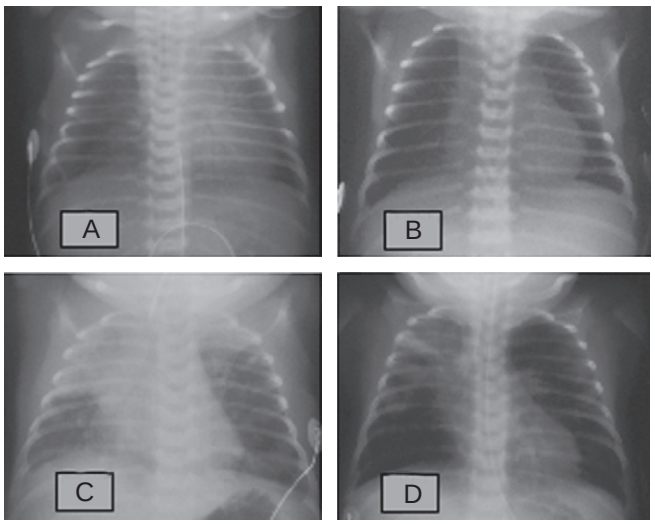

FIGURE 28-1. Chest radiographs from a premature infant who suffered RSV pneumonia early in life. **A,** This infant presented with neonatal respiratory distress syndrome (RDS) requiring mechanical ventilation; the radiograph shows a ground-glass appearance and lung volume loss from RDS on the day of birth. **B,** By 1 week of life, mechanical ventilation is discontinued and the lung fields normalize. **C,** At 6 weeks of life, the infant presented with an RSV-positive test and respiratory distress requiring mechanical ventilation; the radiograph shows diffuse interstitial infiltrates and atelectasis or pneumonia of the right upper lobe. **D,** By 7 weeks of life, the infant remained on a mechanical ventilator, but infiltrates and atelectasis were improving. (Radiographs courtesy of James Crowe, MD, Texas Children's Hospital.)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for nonviral causes of pneumonia varies by age. In newborns, group B streptococcus infection and hyaline membrane disease are the most common considerations. In infants, atypical organisms (e.g., *Chlamydia trachomatis* and *Ureaplasma urealyticum*) must be considered, as well as *Pneumocystis carinii* in children with immunodeficiencies or *in utero* exposure to human immunodeficiency virus. Common bacterial causes of pneumonia are *Bordetella pertussis, Streptococcus pneumoniae, Haemophilus influenzae* (mostly nontypable species in the era of universal immunization against type B), and *Mycobacterium* infections (including tuberculosis). In young children, *Mycoplasma pneumoniae, S. pneumoniae,* and *Mycobacterium* infections are important. In older children and adolescents, the atypical organisms *M. pneumoniae, C. trachomatis,* and *Chlamydia pneumoniae* remain important, and the bacteria *S. pneumoniae, B. pertussis,* and *Mycobacterium* species are considerations. *Histoplasma capsulatum* infection is relatively common in certain areas of the United States and causes an atypical pneumonia. *Cryptococcus neoformans* infection is also a consideration in immunocompromised patients.

Many published studies have addressed the differentiation of bacterial from viral pneumonia using clinical, radiologic, and routine hematologic tests, but these methods have not been found to be sufficiently reliable in differential diagnosis.[23–33]

Chest radiographic findings, total white blood cell count, erythrocyte sedimentation rate, and serum C-reactive protein have been used widely in children with community-acquired pneumonia of varying etiology to discriminate between bacterial and viral causes, but the specificities of these are not sufficient to determine the diagnosis in clinical practice. Lymphocytic predominance

is usually present in the peripheral white blood cells during viral pneumonias, although this feature is also usually present in pertussis and atypical bacterial infections. Bacterial pneumonia requiring hospitalization on average causes higher fever than viral pneumonia, and it is more often associated with a fever higher than 103° F than is viral pneumonia. A lobar, segmental, or rounded well-defined pneumonia affecting a single lobe is more likely to be bacterial in etiology, as are cases associated with large pleural effusions, abscess, bullae, or pneumatoceles. A bedside cold agglutinins test may be positive in the case of viral pneumonia or mycoplasmal infection, thus it is not a particularly helpful test in distinguishing etiology.

LABORATORY DIAGNOSIS OF VIRAL ETIOLOGY

The specific cause of viral pneumonia can be identified by several methods with varying levels of stringency. Culture of virus in cell monolayer cultures is considered the gold standard. Viruses are identified by characteristic cytopathic effect and are confirmed by immunodetection using virus-specific antibodies and fluorescence detection. Culture techniques require a high level of expertise and generally are best performed on fresh specimens (e.g., secretions obtained by nasopharyngeal aspiration or nasopharyngeal swab). Rapid diagnostic tests for RSV and influenzas A and B based on the immunodetection of viral proteins in nasopharyngeal secretions are widely used, but their positive predictive value is more appropriate for use during epidemics, when the prevalence of positive tests is expected to be high. Antigen detection tests are not sensitive enough to determine that a hospitalized patient is no longer shedding infectious virus; therefore, negative tests should not be used to justify termination of contact precautions in a patient with viral pneumonia. Increasingly, clinical detection of viruses is being performed by molecular genetic techniques, such as reverse transcriptase–polymerase chain reaction followed by hybridization or sequence analysis. This technique identifies the presence of viral nucleic acid. Polymerase chain reaction tests tend to be more sensitive than cell culture during the period of viral clearance (1 to 3 weeks after infection). It is not clear how long viral RNAs are present following active infections, but evidence to date shows that they may persist for weeks or months, even when virus can no longer be cultured. Therefore, a positive polymerase chain reaction–based test must be used with caution because in some cases a positive test obtained during an acute pneumonia is actually related to a recent infection. Serology is helpful to diagnose or confirm infection, particularly in the clinical research setting. A four-fold increase in serum antibodies against a virus between the pre-infection period and after infection suggests a specific diagnosis, particularly when testing the binding to targets of functional antibodies. In practice, the use of serologic tests to diagnose the cause of pneumonia is difficult because the increase in antibodies in young children may not achieve a significant level until 6 to 8 weeks or more have passed.

CO-INFECTIONS

Single agents cause most cases of viral pneumonia, but co-infection does occur. Most careful studies in children have found evidence for the presence of two viruses in about 5% to 10% of cases of viral LRTI. There is little direct evidence in immunocompetent individuals that co-infection is characterized by a more severe clinical course than infection with a single agent. Bacterial superinfection does occur, but overt bacterial lung disease during viral pneumonia is unusual. Bacterial complication of viral pneumonia is suggested by an abrupt change in symptoms over several hours with appearance of generalized toxicity, and possibly with new radiographic findings of parenchymal consolidation or pleural effusions. Marked and changed leukocytosis (e.g., >20,000 cells/mm^3 peripheral white blood cells) is suggestive of a bacterial process, but it is not particularly sensitive or specific. *S. pneumoniae, H. influenzae,* and *Staphylococcus aureus* are the most common bacteria involved in the complication of viral pneumonia, and influenza virus pneumonia is the most common viral pneumonia that is complicated by bacterial infection. Vaccine studies with a pneumococcal vaccine in a large population of children showed that a 9-valent bacterial polysaccharide vaccine prevented about one third of viral pneumonia cases, suggesting frequent interactions of bacteria and viruses that are not apparent by current methods of clinical evaluation.[34]

THERAPY

Most infants and children with mild viral pneumonia can be treated symptomatically as outpatients. Oxygen is required if there is grunting, flaring, severe tachypnea, and retractions, or if pulse oximetry indicates oxygen saturation below 90% to 92%, or arterial blood gas measurement indicates depressed Po_2 (<60 to 70 mm Hg). Retention of CO_2 is particularly concerning, especially in the face of tachypnea. Severe respiratory distress, hypoxia, and dehydration are among the indications for hospitalization. Care in the hospital is principally supportive, such as the delivery of supplemental oxygen and intravenous fluids, and the use of mechanical ventilation in the case of respiratory failure. The youngest infants with RSV pneumonia may require monitoring for the risk of apnea, although apnea usually presents near the beginning of the illness. Chest physiotherapy and mucolytics have unproven efficacy in viral pneumonia. If a specific viral diagnosis is made early in the course of illness, there are some antiviral medications available. Licensed drugs for influenza infection include the M2 ion-channel inhibitors amantidine and rimantidine, and the neuraminidase inhibitors oseltamivir and zanamivir. Many influenza viruses are resistant to the ion channel inhibitors, however. These antiviral compounds work best when therapy is initiated in the first days of infection and are particularly relevant for those with immunosuppression or preexisting cardiopulmonary disease. Ribavirin delivered as an aerosol is licensed for treatment of severe RSV infection, but recent studies have questioned its value. Most centers do not routinely treat otherwise healthy infants with RSV pneumonia with ribavirin. RSV intravenous immune

globulin and palivizumab (an intramuscular injectable humanized monoclonal antibody directed against the RSV fusion protein) are available for prophylaxis against RSV disease and are indicated for children with chronic cardiopulmonary disease and other serious risk factors. Clinical trials of therapy of acute disease using these antibody preparations, however, have not shown this treatment to be effective during hospitalization. Antibiotic therapy does not improve the outcome in viral pneumonia and has not been shown to alter the risk of bacterial complication of viral pneumonia as a superinfection. Indiscriminate use of antibiotics in the setting of viral infection causes the selection of antibiotic-resistant bacteria. If secondary infection does occur, usually in hospitalized patients in intensive care units, the selected infecting bacterium may not be susceptible to conventional antibiotics. Therefore, specific diagnosis of the etiology of severe pneumonia suspected to be of viral etiology is warranted to minimize inappropriate antibiotic exposure, even when an antiviral therapeutic option is not anticipated.

COMPLICATIONS

Many of the common sequelae of bacterial pneumonia (e.g., persistent effusions, empyemas, abscess formation, and pneumatoceles) are distinctly uncommon following viral pneumonia. Therefore, the prognosis for most forms of viral pneumonia caused by conventional respiratory viruses is excellent. Most otherwise healthy children with uncomplicated pneumonia recover without sequelae. Complications during influenza pneumonia in children range from acute otitis media, sinusitis, and bacterial tracheitis to rare episodes of encephalitis, myositis, myocarditis, febrile seizures, encephalopathy, or Reyes syndrome. RSV disease is commonly complicated by otitis media. Immunocompromised children, those with underlying cardiopulmonary disease, and neonates are at the highest risk for severe sequelae. Pulmonary hypertension can complicate the course of neonatal pneumonia, and concomitant pulmonary hemorrhage due to vascular damage may follow. Pulmonary interstitial emphysema and other types of gas leaks can occur, especially during mechanical ventilation. Mortality is high in neonatal viral pneumonia, especially in premature infants in whom the disease may resemble severe hyaline membrane disease. Infants with severe viral pneumonia early in life who require mechanical ventilation or treatment with high concentrations of supplemental oxygen are at increased risk of chronic lung disease. Some cases of viral pneumonia, especially those due to rapid-onset severe adenovirus infection, can lead to bronchiolitis obliterans and hyperlucent lung syndrome. The prognosis for pneumonia due to more uncommon causes of viral pneumonia (e.g., varicella-zoster virus, SARS-coronavirus, and measles virus) can be guarded.

PROTECTIVE IMMUNITY

Serum-neutralizing antibodies appear to be most protective of the lower respiratory tract against severe disease caused by viruses. Probably this is a result of the close association of the intravascular space with the alveolus. The gradient of antibody transfer to the nasopharynx is quite steep in that there are about 300-fold higher levels of immunoglobulin G (IgG) antibodies in the serum than in the nasopharynx, but levels of IgG in the alveolus and serum can be quite similar.

High levels of IgG in the alveolus are probably caused by transudation. In higher areas of the airway, IgG antibodies may be transported to the lumen by the neonatal Fc receptor. Secretory IgA is uniquely suited for antiviral activity at the respiratory mucosal surface. Mucosal antibody secretion occurs locally, and polymeric IgA is taken up specifically by the polyimmunoglobulin receptor at the base of polarized epithelial cells, transcytosed in the apical direction, and secreted onto the mucosa. Antibodies may contribute to the resolution of acute primary infection of the lung. IgA and IgG RSV antibodies are present in the nasal secretions of infants early in infection, and the decrease in virus shedding in infants infected with RSV has been associated temporally with the detection of RSV-specific IgA in nasal washes. Laboratory studies and clinical trials provide strong evidence for the dominant role of antibodies in protection against re-infection. Maternal antibodies do not cross the placenta efficiently before 32 weeks gestation; therefore, premature infants are lacking the serum antibody protection against viral pneumonia that is conferred to term infants.

Cell-mediated immunity probably plays a primary role in the clearance of established respiratory virus pneumonia in humans. The best evidence to support this concept is that patients with defects in cellular immunity (e.g., recipients of hematopoietic stem cell transplantation or patients with cancer undergoing immunosuppressive chemotherapy) suffer more prolonged virus shedding or more frequent and more severe illnesses with RSV, MPV, influenza virus, or PIV type 3. The role in humans of cell-mediated immune effectors in protection against disease on re-infection or during virus challenge following immunization is less clear, however. Macrophages are abundant in the alveolar spaces of the lung. *In vitro* and *in vivo* data suggest that the resident pulmonary alveolar macrophage population actively suppresses the antigen-presenting function of lung dendritic cells (DCs) *in situ*. Low numbers of DCs and high numbers of macrophages have been noted in the human alveolar compartment, suggesting that the alveolar compartment may be less efficient for mounting an immune response. Human alveolar macrophages recovered during RSV infection can yield small amounts of RSV, but replication of RSV in alveolar macrophages is restricted. Inoculation of human alveolar macrophages with live or inactivated RSV induces increased secretion of cytokines, such as tumor necrosis factor, IL-6, IL-8, and IL-10.

Dendritic cells are distributed widely in the lung, where they are distinguished by their morphology and class II major histocompatibility complex antigen expression. DCs serve as potent pulmonary antigen-presenting cells. However, relatively little is currently known about how these cells respond to specific respiratory viruses at the mucosa. Recruitment of a wave of DCs into the respiratory tract mucosa appears to be a feature of the acute cellular response to local challenge with viral protein

antigens or virus infection. Differentiation of DCs in the lung, homing of particular types of DCs to the lung, and crosstalk between adaptive immune cells and DCs in the lung are all areas of current research.

PREVENTION

The viruses that commonly cause viral pneumonia are ubiquitous, and every child becomes infected in the first years of life with most of the common respiratory viruses. It is not feasible to avoid or prevent exposure or infection completely; therefore, the practical goal is to avoid infection at a time of high risk and to prevent severe disease or complications during infection. Thorough hand hygiene, the use of contact isolation, and patient or provider cohorting are critical to the prevention of the nosocomial spread of infection to high-risk individuals in the hospital. Vaccination of at-risk individuals with licensed vaccines for seasonal influenza virus is wise. Influenza antivirals can be used effectively as a prophylactic treatment in some for the prevention of symptomatic influenza disease during an epidemic or immediately following exposure. Prophylactic treatments with an RSV monoclonal antibody (palivizumab, IM) can be used in infants at high risk of RSV disease, and these treatments prevent half or more of RSV hospitalizations during treatment. The combination of risk factors that best predicts susceptibility to hospitalization due to RSV is not entirely clear, but includes extreme prematurity, bronchopulmonary disease, and oxygen dependence. More subtle influences are important, but they affect risk incrementally. The use of the live attenuated measles-mumps-rubella vaccine is effective against measles and mumps disease, and varicella vaccine prevents severe disease caused by that virus. An adenovirus vaccine has been used effectively, but only in the military to prevent epidemic disease in adults who live in close quarters.

EXPERIMENTAL VACCINES

Candidate vaccines have been developed and tested for prevention of viral pneumonia caused by RSV; PIV types 1, 2, and 3; and hMPV. Both subunit and live attenuated RSV vaccines have been tested in phase I or II trials, and the live attenuated vaccines appear promising. The challenge for investigators is to identify or generate attenuated viruses that are sufficiently immunogenic to induce a protective response in newborns without causing any signs or symptoms of respiratory disease. Cold-passaged or bovine strain PIV type 3 vaccines have been tested extensively in humans, and they appear promising. To date, HMPV vaccine candidates have been generated, but they have not been tested in clinical trials.

References

The complete reference list is available online at www.expertconsult.com