Chapter **260**

Respiratory Syncytial Virus

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Respiratory syncytial virus (RSV) is the major cause of bronchiolitis (see Chapter 391) and viral pneumonia in children younger than 1 yr of age and is the most important respiratory tract pathogen of early childhood.

ETIOLOGY

RSV is an enveloped RNA virus with a single-stranded negative-sense genome that replicates entirely in the cytoplasm of infected cells and matures by budding from the apical surface of the cell membrane. Because this virus has a nonsegmented genome, it cannot undergo antigenic shift by reassortment like the influenza viruses do. The virus belongs to the family Paramyxoviridae, along with parainfluenza and measles viruses, and is in the subfamily Pneumovirinae, which also contains the human metapneumovirus (see Chapter 261). It is the only member of the genus *Pneumovirus* that infects humans. There are 2 antigenic subgroups of RSV, distinguished based primarily on variation in 1 of the 2 surface proteins, the G glycoprotein that is responsible for attachment. This antigenic variation caused by point mutations from infidelity of the virus RNA polymerase may to some

degree contribute to the frequency with which RSV reinfects children and adults.

RSV replicates in a wide variety of cell line monolayer cultures in vitro, and in HeLa or HEp-2 cells produces characteristic syncytial cytopathology, from which the virus derives its name. Interestingly, it is now known that the virus does not cause large syncytia in polarized epithelial cells in vitro, and it is not clear whether syncytium formation occurs to any significant degree in vivo.

EPIDEMIOLOGY

RSV is distributed worldwide and appears in yearly epidemics. In temperate climates, these epidemics occur each winter over 4-5 mo. During the remainder of the year, infections are sporadic and much less common. In the Northern hemisphere, epidemics usually peak in January, February, or March, but peaks have been recognized as early as December and as late as June. Some areas in the United States, such as Florida, report a moderate incidence year-round. In the Southern hemisphere, outbreaks also occur during winter months in that hemisphere. RSV outbreaks often overlap with outbreaks of influenza and human metapneumovirus but are generally more consistent from year to year and result in more disease overall, especially among infants younger than 6 mo of age. In the tropics, the epidemic pattern is less clear. This pattern of widespread annual outbreaks and the high incidence of infection during the 1st 3-4 mo of life are unique among human viruses.

Transplacentally acquired anti-RSV maternal immunoglobulin G serum antibodies, if present in high concentration, appear to provide partial but incomplete protection. These immunoglobulin Gs may account for the lower severity of RSV infections during the 1st 4-6 wk of life, except among infants born prematurely, who receive less maternal immunoglobulin. Breastfeeding provides substantial protection against severe disease, an effect that may pertain only to female infants and not male infants. RSV is one of the most contagious viruses that affect humans. Infection is nearly universal among children by their 2nd birthday. Reinfection occurs at a rate of at least 10-20% per epidemic throughout childhood, with a lower frequency among adults. In situations of high exposure, such as daycare centers, attack rates are nearly 100% among previously uninfected infants and 60-80% for second and subsequent infections.

Reinfection may occur as early as a few weeks after recovery, but usually takes place during subsequent annual outbreaks. Antigenic variation is not required for reinfection, as shown by the fact that a proportion of adults inoculated repeatedly with the same experimental preparation of wild-type virus could be reinfected multiple times. The immune response of infants is poor in quality, magnitude, and durability. The severity of illness during reinfection in childhood is usually lower and appears to be a function of partial acquired immunity, more robust airway physiology, and increased age.

Asymptomatic RSV infection is unusual in young children. Most infants experience coryza and pharyngitis, often with fever and frequently with otitis media caused by a virus in the middle ear or bacterial superinfection following eustachian tube dysfunction. The lower respiratory tract is involved to a varying degree with bronchiolitis and bronchopneumonia in about a third of children. The hospitalization rate for RSV infection in otherwise healthy infants is typically 0.5-4%, depending on region, gender, socioeconomic status, exposure to cigarette smoke, gestational age, and family history of atopy. The admitting diagnosis is usually bronchiolitis with hypoxia, although this condition is often indistinguishable from RSV pneumonia in infants, and, indeed, the 2 processes frequently coexist. All RSV diseases of the lower respiratory tract (excluding croup) have their highest incidence at 6 wk to 7 mo of age and decrease in frequency thereafter. The syndrome of bronchiolitis is much less common after the 1st birthday. The terminology used for diagnosis of virus-associated wheezing illnesses in toddlers is confusing, as these illnesses are variably termed *wheezing-associated respiratory infection,* *"wheezy bronchitis,"* exacerbation of *reactive airways disease,* or *asthma attack*. Because many toddlers wheeze during RSV infection but do not go on to have lifelong asthma, it is best to use the diagnostic term *asthma* only later in life. Acute viral

pneumonia is a recurring problem throughout childhood, although RSV becomes less prominent as the etiologic agent after the 1st yr. RSV plays a causative role in an estimated 40-75% of cases of hospitalized bronchiolitis, 15-40% of cases of childhood pneumonia, and 6-15% of cases of croup.

Bronchiolitis and pneumonia resulting from RSV are more common in boys than in girls by a ratio of approximately 1.5:1. Other risk factors with similar impact include 1 or more siblings in the home, white race, rural residence, maternal smoking, and maternal education <12 yr. The medical factors in infants associated with highest risk are chronic lung disease of prematurity, congenital heart disease, immunodeficiency, and prematurity. Still, most infants admitted to the hospital because of RSV infection do not have strong, easily identifiable risk factors. Therefore, any strategy for prophylaxis focused only on individuals with strong risk factors probably could prevent only approximately 10% of hospitalizations, even if the prophylaxis was 100% effective in treated high-risk individuals.

The incubation period from exposure to first symptoms is approximately 3-5 days. The virus is excreted for variable periods, probably depending on severity of illness and immunologic status. Most infants with lower respiratory tract illness shed infectious virus for 1-2 wk after hospital admission. Excretion for 3 wk, and even longer, has been documented. Spread of infection occurs when large, infected droplets, either airborne or conveyed on hands or other fomites, are inoculated in the nasopharynx of a susceptible subject. RSV is probably introduced into most families by young schoolchildren undergoing reinfection. Typically, in the space of a few days, 25-50% of older siblings and 1 or both parents acquire upper respiratory tract infections, but infants become more severely ill with fever, otitis media, or lower respiratory tract disease.

Nosocomial infection during RSV epidemics is an important concern. Virus is usually spread from child to child on the hands of caregivers or other fomites. Adults undergoing reinfection also have been implicated in spread of the virus. Contact precautions are sufficient to prevent spread when compliance is meticulous, as the virus is not usually spread by small particle aerosol. In practice, however, adherence to isolation procedures by caregivers often is not complete.

PATHOGENESIS

Bronchiolitis is caused by obstruction and collapse of the small airways during expiration. Infants are particularly apt to experience small airway obstruction because of the small size of their normal bronchioles; airway resistance is proportional to $1/radius^4$. There has been relatively little pathologic examination of RSV disease in the lower airways of otherwise healthy subjects. Airway narrowing likely is caused by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round-cell infiltration and edema of the surrounding submucosa. These changes result in formation of mucus plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia, the infiltration is more generalized, and epithelial shedding may extend to both the bronchi and the alveoli. In older subjects, smooth muscle hyperreactivity may contribute to airway narrowing, but the airways of young infants typically do not exhibit a high degree of reversible smooth muscle hyperreactivity during RSV infection.

Several facts suggest that elements of the host response may cause inflammation and contribute to tissue damage. The immune response required to eliminate virus-infected cells is a double-edged sword, reducing the cells producing virus but causing host cell death in the process. A large number of soluble factors, such as cytokines, chemokines, and leukotrienes, are released in the process, and skewing of the patterns of these responses may predispose some individuals to more severe disease. There is also evidence that genetic factors may predispose to more severe bronchiolitis.

Children who received a formalin-inactivated, parenterally administered RSV vaccine in the 1960s experienced more severe and more frequent bronchiolitis upon subsequent natural exposure to wild-type RSV than did their age-matched controls. Several children died during naturally acquired RSV infection after vaccination. This event has greatly inhibited progress in RSV vaccine development, because of both an incomplete understanding of the mechanism and a reluctance to test new experimental vaccines that might induce the same type of response.

Some studies have identified the presence of both RSV and human metapneumovirus viral RNA in airway secretions in a significant proportion of infants requiring assisted ventilation and intensive care. It may be that coinfection is associated with more severe disease. Positive results of polymerase chain reaction (PCR) analysis must be interpreted carefully because this positivity can remain for prolonged periods after infection, even when infectious virus can no longer be detected.

It is not clear how often superimposed bacterial infection plays a pathogenic role in RSV lower respiratory tract disease. RSV bronchiolitis in infants is probably exclusively a viral disease, although there is evidence that bacterial pneumonia can be triggered by respiratory viral infection, including with RSV. A large clinical study of pneumococcal vaccine showed that childhood vaccination reduced the incidence of viral pneumonia by approximately 30%, suggesting viral-bacterial interactions that we currently do not fully understand.

CLINICAL MANIFESTATIONS

Typically, the first sign of infection in infants with RSV is rhinorrhea. Cough may appear simultaneously but more often does so after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child who experiences bronchiolitis begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse fine inspiratory crackles and expiratory wheezes. Rhinorrhea usually persists throughout the illness, with intermittent fever. Chest radiograph findings at this stage are frequently normal.

If the illness progresses, cough and wheezing worsen and air hunger ensues, with increased respiratory rate, intercostal and subcostal retractions, hyperexpansion of the chest, restlessness, and peripheral cyanosis. Signs of severe, life-threatening illness are central cyanosis, tachypnea of >70 breaths/min, listlessness, and apneic spells. At this stage, the chest may be significantly hyperexpanded and almost silent to auscultation because of poor air movement.

Chest radiographs of infants hospitalized with RSV bronchiolitis have normal findings in approximately 30% of cases, with the other 70% showing hyperexpansion of the chest, peribronchial thickening, and interstitial infiltrates. Segmental or lobar consolidation is unusual and pleural effusion is rare.

In some infants, the course of the illness may resemble that of pneumonia, the prodromal rhinorrhea and cough being followed by dyspnea, poor feeding, and listlessness, with a minimum of wheezing and hyperexpansion. Although the clinical diagnosis is pneumonia, wheezing is often present intermittently and the chest radiographs may show air trapping.

Fever is an inconstant sign in RSV infection. In young infants, particularly those who were born prematurely, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. Apnea is not necessarily caused by respiratory exhaustion, but rather appears to be a consequence of alterations in central control of breathing.

RSV infections in profoundly immunocompromised hosts may be severe at any age of life. The mortality rates associated with RSV pneumonia in the 1st few wk after hematopoietic stem cell or solid organ transplantation in both children and adults are high. RSV infection does not seem to be more severe in HIV-infected patients with reasonable control of HIV disease, although these patients may shed virus for prolonged periods.

DIAGNOSIS

Bronchiolitis is a clinical diagnosis. RSV can be suspected with varying degrees of certainty on the basis of the season of the year and the presence of the virus in the community. Other epidemiologic features that

may be helpful are the presence of colds in older household contacts and the age of the child. The other respiratory viruses that attack infants frequently during the 1st few mo of life are parainfluenza virus type 3, human metapneumovirus, enteroviruses, coronaviruses, and influenza viruses. Rhinovirus is frequently found in the respiratory tract of children, and there is growing evidence that this virus may contribute significantly to lower respiratory tract disease.

Routine laboratory tests are of minimal diagnostic use in most cases of bronchiolitis or pneumonia caused by RSV. The white blood cell count is normal or elevated, and the differential cell count may be normal with either a neutrophilic or mononuclear predominance. Hypoxemia as measured by pulse oximetry or arterial blood gas analysis is frequent and tends to be more marked than anticipated from the clinical findings. A normal or elevated blood CO_2 value in a patient with a markedly elevated respiratory rate is a sign of respiratory failure.

The most important diagnostic concern is to identify bacterial or chlamydial involvement. When bronchiolitis is not accompanied by infiltrates on chest radiographs, there is little likelihood of a bacterial component. In infants 1-4 mo of age, interstitial pneumonitis may be caused by *Chlamydia trachomatis* (see Chapter 226). With *C. trachomatis* pneumonia there may be a history of conjunctivitis, and the illness tends to be of subacute onset. Coughing and inspiratory crackles may be prominent; wheezing is not. Fever is usually absent.

Lobar consolidation without other signs or with pleural effusion should be considered of bacterial etiology until proved otherwise. Other signs suggesting bacterial pneumonia are neutrophilia, neutropenia in the presence of severe disease, ileus or other abdominal signs, high temperature, and circulatory collapse. In such instances, antibiotics should be initiated.

Definitive diagnosis of RSV infection is based on the detection in respiratory secretions of live virus by cell culture. The presence of viral RNA (detected by a molecular diagnostic test using reverse transcription PCR) or viral antigens (detected by a rapid diagnostic test, usually a membrane blotting test incorporating antibody detection of viral proteins) is strongly supportive in the right clinical setting. The antigen test is less sensitive than culture, whereas reverse transcription PCR analysis is more sensitive than culture. An aspirate of mucus or a nasopharyngeal wash from the child's posterior nasal cavity is the optimal specimen. Nasopharyngeal or throat swabs are less preferable but acceptable. A tracheal aspirate is unnecessary, but endotracheal tube lavage fluid from patients intubated for mechanical ventilation can be tested. The specimen should be placed on ice, taken directly to the laboratory, and processed immediately for culture, antigen detection, or PCR analysis. The virus is thermolabile, so it degrades over relatively short periods of time unless frozen at a low temperature such as −80°C (−112°F) in freezers used in research settings.

TREATMENT

The treatment of uncomplicated cases of bronchiolitis is symptomatic. Humidified oxygen and suctioning are usually indicated for hospitalized infants who are hypoxic. Many infants are slightly to moderately dehydrated, and therefore fluids should be carefully administered in amounts somewhat greater than those for maintenance. Often, intravenous or tube feeding is helpful when sucking is difficult because of tachypnea.

There is disagreement among experts regarding the usefulness of aerosolized saline or hypertonic saline, epinephrine or β_2-agonists in RSV bronchiolitis. Most patients do not receive lasting benefit from prolonged therapy, which is associated with a relatively high frequency of side effects. Corticosteroid therapy is not indicated except in older children with an established diagnosis of asthma, because its use is associated with prolonged virus shedding and is of no proven clinical benefit.

In nearly all instances of bronchiolitis, antibiotics are not useful, and their inappropriate use contributes to development of antibiotic resistance. Interstitial pneumonia in infants 1-4 mo old may be caused by *C. trachomatis,* and macrolide therapy may be indicated for that infection.

Ribavirin is an antiviral agent delivered through an oxygen hood, face mask, or endotracheal tube with use of a small-particle aerosol

generator most of the day for 3-5 days. Early small trials of its use suggested a modest beneficial effect on the course of RSV pneumonia, with some reduction in the duration of both mechanical ventilation and hospitalization. However, subsequent studies failed to document a clear beneficial effect of ribavirin, and therefore this drug is no longer used for routine therapy of RSV disease. The monoclonal antibody palivizumab is licensed for prophylaxis in high-risk infants during the RSV season, and does prevent about half of the expected hospitalizations in that population. Small clinical trials using the palivizumab as a therapy during established infection have not shown benefit to date.

PROGNOSIS

The mortality rate of hospitalized infants with RSV infection of the lower respiratory tract is very low in the developed world. Almost all deaths occur among young, premature infants or infants with underlying disease of the neuromuscular, pulmonary, cardiovascular, or immunologic system. It is estimated, however, that more than 100,000 children worldwide in resource-poor settings die each year from RSV. In addition, thousands of elderly patients die of RSV infection each year in the United States.

Many children with asthma have a history of bronchiolitis in infancy. There is recurrent wheezing in 30-50% of children with severe RSV bronchiolitis in infancy. The likelihood of recurrence is increased in the presence of an allergic diathesis (e.g., eczema, hay fever, or a family history of asthma). With a clinical presentation of bronchiolitis in a patient older than 1 yr of age, there is an increasing probability that, although the episode may be virus induced, this is likely the first of multiple wheezing attacks that will later be diagnosed as hyperreactive airways disease or asthma. Asthma is difficult to diagnose in the 1st yr of life. It is not fully clear at this time whether early, severe RSV wheezing disease causes some cases of asthma or whether subjects destined to suffer asthma present with symptoms first when provoked by RSV infection during infancy. However, results from a recent long-term follow-up study of infants who received palivizumab prophylaxis suggested that prevention of severe RSV infection reduces the incidence of reactive airways disease later in life.

PREVENTION

In the hospital, the most important preventive measures are aimed at blocking nosocomial spread. During RSV season, high-risk infants should be separated from all infants with respiratory symptoms. Gowns, gloves, and careful handwashing should be used for the care of all infants with suspected or established RSV infection. A high level of compliance with contact isolation is essential. Viral laboratory tests are adequate for diagnosis in the setting of acute disease when levels of virus are high, but they are not designed to detect low levels of virus. Therefore, contact precaution isolation should be observed for most patients admitted for acute disease assigned for the duration of hospitalization; rapid antigen tests should not be used to determine whether or not a patient still requires isolation. Ideally, patients with RSV or metapneumovirus infections are housed separately, because coinfection may be associated with more severe disease.

Passive Immunoprophylaxis

Administration of palivizumab (15 mg/kg IM once a month), a neutralizing humanized murine monoclonal antibody against RSV, is recommended for protecting high-risk children against serious complications from RSV disease. Immunoprophylaxis reduces the frequency and total days of hospitalization for RSV infections in high-risk infants in about half of cases. Palivizumab is administered monthly from the beginning to the end of the RSV season. The American Academy of Pediatrics Committee on Infectious Diseases issued "Modified Recommendations for Use of Palivizumab for Prevention of Respiratory Syncytial Virus Infections" in 2014. Palivizumab prophylaxis may be considered for the following infants and children
- Infants born before 29 wk of gestation in the 1st yr of life
- Infants born before 32 wk of gestation, who have chronic lung disease of prematurity (required >21% FIO_2 [fraction of inspired oxygen] for ≥28 days after birth), in the 1st yr of life

- Infants younger than 1 yr of age with hemodynamically significant congenital heart disease
- Children 24 mo of age or younger with profound immunocompromising conditions during RSV season
- Infants in the 1st yr of life who have either congenital abnormalities of the airway or neuromuscular disease that compromises handling of respiratory secretions
- Administration in the 2nd yr of life is recommended for children who required 28 or more days of oxygen after birth and who have ongoing treatment for chronic pulmonary disease (oxygen, steroids, diuretics)

The American Academy of Pediatrics 2012 *Red Book* recommendations also give the following specific guidelines on implementation of prophylaxis. Recommendations for initiation and termination of prophylaxis reflect current descriptions from the Centers for Disease Control and Prevention of RSV seasonality in different geographic locations within the United States. Typically, prophylaxis is initiated July 1 in southeast Florida, September 15 in north-central and southwest Florida, and November 1 in most other areas of the United States. Regardless of the month in which the 1st dose is administered, the recommendation for a maximal number of 5 doses for all geographic locations is emphasized for infants with hemodynamically significant congenital heart disease, chronic lung disease of prematurity, or birth before 32 wk, 0 days of gestation. A maximal number of 3 doses is recommended for infants with a gestational age of 32 wk, 0 days to 34 wk, 6 days without hemodynamically significant congenital heart disease or chronic lung disease of prematurity who qualify for prophylaxis. Infants born from 32 wk, 0 days through 34 wk, 6 days of gestation who qualify for prophylaxis under the new recommendations should receive prophylaxis only until they reach 90 days of age or a maximum of 3 doses (whichever comes first).

Vaccine

There is no licensed vaccine against RSV. The challenge for development of live virus vaccines has been to produce attenuated vaccine strains that infect infants in the nasopharynx after topical inoculation without producing unacceptable symptoms, that remain genetically stable during shedding, and that induce protection against severe disease following reinfection. The most promising live-attenuated virus candidates have been engineered in the laboratory from cold-passaged strains of RSV, according to a basic strategy that yielded the live poliovirus and influenza virus vaccine strains. A variety of nonreplicating experimental vaccines are being tested in early clinical trials. Plans are underway to study some of the new vaccine candidates in maternal immunization trials. The rationale of such studies is to test whether boosting the serum level of RSV-neutralizing antibodies in the mother can enhance immunity in neonates following transplacental transfer of maternal antibodies to the infant.

Bibliography is available at Expert Consult.

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