Respiratory Syncytial Virus

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Name of Virus: Respiratory Syncytial Virus

11.1 Brief Introduction

Clinically known for about a century but not isolated until 1956, respiratory syncytial virus (RSV) represents the most common cause of bronchiolitis, outranking all other microbial pathogens as a cause of pneumonia or bronchiolitis in infants under the age of one. However, its frequency in adults, particularly debilitated adult patients, is on the rise. The virus name is derived from its ability to produce cell fusion (syncytia) in tissue culture media (Morris et al. 1956; Papenburg and Boivin 2010).

Synonyms: RSV pneumonia, HRSV pneumonia

11.2 Classification

Family – *Paramyxoviridae*
Genus – *Pneumovirus*

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11.3 Epidemiology

RSV infections are prevalent worldwide. In temperate climates, RSV infections occur as annual community outbreaks, often lasting several months during late fall, winter, and early spring. RSV is spread from respiratory secretions through close contact with infected persons or contact with contaminated surfaces or objects. RSV is unstable in the environment, surviving only a few hours on environmental surfaces, and it is readily inactivated with soap and water (Ryan and Ray 2010; Zaki and Paddock 2001, 2008).

11.4 Ultrastructure

The RSV virion is similar to parainfluenza viruses and consists of a nucleocapsid that is packaged in a lipid envelope derived from the host cell plasma membrane during budding. When visualized by electron microscopy, virions appear as irregular spheroidal particles, 100–350 nm in diameter. The nucleocapsid is a symmetric helix that sometimes can be seen in cross section as electron dense dots. RSV is morphologically indistinguishable from other *Paramyxoviridae* when viewed by negative-contrast electron microscopy (Bachi and Howe 1973; Zaki and Paddock 2008).

11.5   Immunology

At least two antigenic subgroups (A and B) of RSV are known to exist. This antigenic dimorphism is due primarily to difference in the surface G glycoproteins. Two surface glycoproteins, G and F, are present in the envelope and mediate attachment and fusion with cells of the respiratory epithelium. The F proteins also mediate coalescence of neighboring cells to form the characteristic syncytial cells for which the virus receives its name (Ryan and Ray 2010). The epidemiologic and biologic significance of the two antigenic variants of RSV is uncertain. However, there is some evidence to suggest that Group A infections tend to be more severe (Domachowske and Rosenberg 1999; Ryan and Ray 2010).

11.6   Clinical Features

Infections with RSV are seasonal, with onset in winter to early spring. The incubation period of RSV pneumonia in very young infants is 2–4 days. The incubation period is followed by rhinitis and, in quick succession, within 1–3 additional days, by manifestations of bronchiolitis or pneumonitis. Manifestations of both bronchiolitis and pneumonia include fever, cough, and dyspnea. These manifestations are age related and tend to be severe in infants. The overall duration of the illness is up to 14 days. Older infants, children, and adults are also readily infected, but the disease in these age groups tends to be milder. One exception is elderly adult patients, who are prone to experience considerable morbidity. The greater severity of the disease in infants is believed to be related to inherent narrow airways and further narrowing of the tracheobronchial tree brought about by mucosal swelling.

An important subset of children with RSV infection presents with asthma-like signs of bronchial hyperresponsiveness. Studies to date have shown a significant connection between RSV infection and childhood asthma (Mohapatra and Boyapalle 2008). This connection is more applicable to children experiencing RSV bronchiolitis during the first decade of life as opposed to older children. The nature of the asthma-like features of RSV infection has not been elucidated, but a common pathogenetic mechanism between RSV infection and asthma involving molecules derived from eosinophiles such as major basic protein and eosinophilic cationic protein may be at play (Ishioka et al. 2011). Radiographic changes include multifocal air space consolidation and peribronchial thickening. In adults, bilateral interstitial opacities and multifocal consolidation are present (Zaki and Paddock 2008).

11.7   Pathologic Changes

In contrast to other viruses such as influenza that affect multiple organs and systems, RSV infections are limited to the respiratory tract. In RSV, the lungs may be heavy and diffusely firm and may show areas of atelectasis. Large and small airways can contain necrotic debris and mucus and may show mucosal ulcerations. Within a short time of infection, a striking interstitial mononuclear (chiefly lymphocytic) pneumonia develops. The virus replicates in the cytoplasm of epithelial cells and after maturation buds off from cell membranes, spreading to neighboring cells. The epithelial cells swell, desquamate, and die, mixing with mucoid secretions and forming casts that partially or completely block the lumen of smaller airways (Haselton 1996). Cases with associated diffuse alveolar damage do occur. In addition, organizational changes and secondary bacterial superinfection may supervene (Zaki and Paddock 2001). Giant cell pneumonia with numerous multinucleated giant cells is characteristic but not pathognomonic, as it may occur in other conditions including aspiration pneumonitis and other viral pneumonias (see differential diagnosis below). The multinucleated giant cells contain many somewhat peripherally distributed nuclei. These inclusions may be inconspicuous and may be difficult to identify with any degree of certainty. The diagnosis of RSV pneumonia
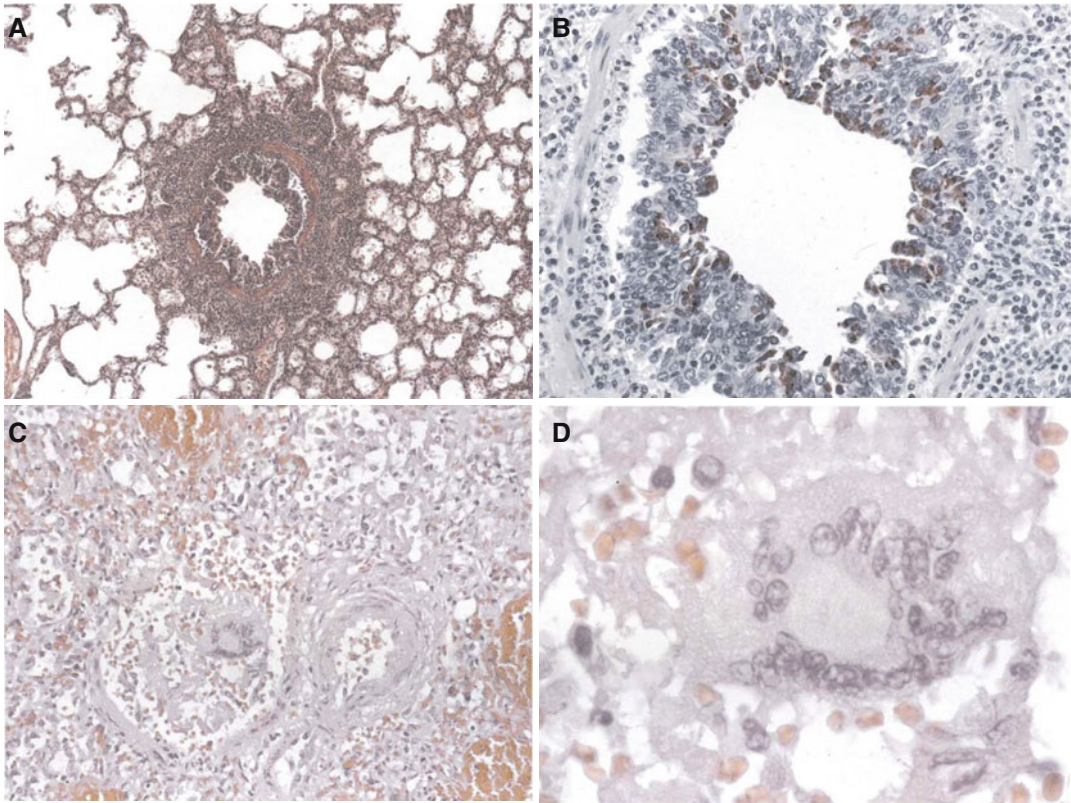
Fig. 11.1 *Panel A:* Respiratory syncytial virus pneumonia. Note cuff-like intense bronchiolar and peribronchiolar inflammatory reaction. Hematoxylin and eosin. *Panel B:* Same bronchiole illustrated in *Panel A* showing RSV antigen. Immunoalkaline phosphatase staining with naphthol fast red and hematoxylin counterstain. *Panel C:* Note severe pneumonia with interstitial inflammation, hemorrhage, and multinucleated giant cells. Hematoxylin and eosin stain. *Panel D:* Closer view showing large multinucleated giant cells lacking unequivocal viral inclusions. Hematoxylin and eosin stain (*Courtesy of Drs. Zaki and Paddock, Centers for Disease Control and Prevention, Atlanta, GA; from Dail and Hammar's Pulmonary Pathology, 3rd ed, Ch 11 Viral Infections of the Lung, by Tomashefski, with kind permission of Springer Science + Business Media)

can be made with some assurance when variably sized but generally small, irregular, slightly granular, and weakly eosinophilic inclusions are found in the cytoplasm of alveolar and/or bronchiolar epithelial cells (Fig. 11.1) (Sherri's Medical Micro 2010; Zaki and Paddock 2001, 2008).

11.8 Diagnosis

Definitive diagnosis depends on laboratory confirmation. The most definitive test is isolation of the virus in cell culture media. RSV grows in HEp2 cells, HeLa cells, and cells adapted from type II human alveolar epithelial carcinoma cells, known as A549. Optimal specimens can be obtained by gentle aspiration of nasal or nasopharyngeal secretions or more commonly by nasal swabs. RSV can also be detected in macrophages recovered from BAL fluids or from epithelial cells of patients with a background of marrow, heart, lung, or renal transplants (Collins and Crowe 2002; Haselton 1996). In addition to viral isolation, the diagnosis can be established by direct detection of viral antigen in clinical specimens, using enzyme-linked immunoassay, immunofluorescence, immunohistochemistry, or detection of

viral RNA by RT-PCR or by demonstration of a rise in RSV-specific serum antibodies. The virus is extremely labile and does not survive long, and attempts at culture isolation may fail if there is a delay in the submission of the clinical specimen to the laboratory (Zaki and Paddock 2008). Another diagnostic modality is ultrastructural analysis of the virion. An analysis showing pleomorphic features, size within recognized limits (see above), and numerous 12 nm glycoprotein spikes coupled with appropriate clinical and serological data can be regarded as consistent with RSV infection. In our laboratory we screen specimens with a solid-phase EIA, a test that has good specificity and a rapid (less than 1 h) turnaround time. In the event of a negative EIA result, we proceed with a more sensitive test such as direct immunofluorescence (DFA), viral culture, or molecular testing. The sensitivity of DFA is comparable to that of viral culture and, if positive, can be regarded as diagnostic.

11.9   Differential Diagnosis

Clinically, the differential diagnosis includes pneumonia caused by adenoviruses, rhinoviruses, enteroviruses, and influenza viruses as well as infections by *Chlamydia trachomatis*, particularly in infants younger than 4 months. In HIV-infected children, infection by *Pneumocystis jiroveci* should also be considered (Collins and Crowe 2002). Viral pneumonias other than RSV pneumonia can be manifested histopathologically as inflammatory processes containing large or giant multinucleated giant cells. These pneumonias include measles, parainfluenza, and varicella/herpes zoster pneumonias. Human metapneumovirus (MPV) produces changes comparable to RSV and should also be included in the differential diagnosis (Kradin and Mark 2010). A helpful hint is that children in pediatric ICUs infected with MPV are likely to be older than those with RSV infection and more likely to present with pneumonia rather than a bronchiolitis type of illness (Paget et al. 2011).

11.10   Prevention

Patients with increased risk of severe or fatal infection include premature infants with congenital heart or lung disease and children with cystic fibrosis or severe immunodeficiency. See vaccination below.

11.11   Treatment and Outcome

Currently, there is no effective vaccine against RSV, but prophylaxis with neutralizing antibodies appears to reduce the need for hospitalization and to be the best method for preventing severe disease. Inhaled ribavirin is effective and has been approved for use in the management of hospitalized infants and young children with severe lower respiratory tract infections. The role of ribavirin in adults is less well documented, but some reports indicate favorable results in adults with RSV infections. An exception is RSV infection associated with clinical ARDS syndrome in previously healthy adults. In this setting, the mortality rate is very high, 40–60 % as reported by Luo et al. (2011). However, some of these patients may also respond to ribavirin with clinical improvement and restoration of pulmonary function to near normal levels, as reported by the same authors (Luo et al. 2011).

11.12   Vaccine

In the 1960s, a formalin-inactivated RSV vaccine trial was implemented. Regrettably, the trial led to exacerbation of disease and two reported deaths (Blanco et al. 2010). Since then interest in the development of live attenuated vaccines has been maintained, but the genetic and immunological components of the hosts that led to death in two individuals during the 1960s trial remain an enigma (Blanco et al. 2010).

Multiple classical approaches for the development of an effective vaccine against RSV have been so far unsuccessful (McLlelan et al. 2010),

and alternative methodologies are clearly needed. Chang et al. have evaluated current progress made on the development of a successful RSV vaccine (Chang 2011). Hurdles apparently operative on the development of an effective vaccine include incomplete immunity to natural infection leading to reinfection, the immaturity of the immune system in the young, the effect of protective maternal antibodies in the subject primary population (infants), and an imbalanced Th-2-biased immune response to some vaccine candidates, leading to adverse pathologic changes (Chang 2011).

11.13   Clinicopathologic Capsule

A ubiquitous acute respiratory illness with worldwide distribution, RSV is prone to present as community outbreaks in late fall, winter, and early spring. Ultrastructurally, the viral agent, a member of the family *Paramyxoviridae*, shows unique spheroidal particles and long filamentous forms. Two antigenic groups are recognized, A and B. RSV subgroup A appears to be more virulent. Clinically, the illness is an acute type of bronchiolitis that may progress to pneumonia. The histopathologic hallmark is an interstitial pneumonia with multiple multinucleated (syncytial) giant cells. The differential diagnosis rests upon exclusion of other acute viral pneumonias, particularly measles, parainfluenza, and varicella/herpes zoster pneumonia. A definitive diagnosis can be made by isolation of the virus in cell culture media. Ribavirin is an effective agent in children, but its usefulness in adults has not been clearly documented. A safe effective vaccine is not available, but prophylaxis with neutralizing antibodies can help to reduce the need for hospitalization in some children.

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