### 17.1 Brief Introduction

Viruses are the predominant cause of lower respiratory tract illness in infants and a major cause of hospitalization in this vulnerable population. This chapter will review the common respiratory viral agents in infants and young children, including epidemiology and clinical and radiographic features. The role of the laboratory in diagnosis is emphasized with respect to rapid diagnostic techniques and histopathologic features in tissue sections. A brief summary of each of the major infantile respiratory viruses is provided, including respiratory syncytial virus, parainfluenza virus, adenovirus, and influenza virus, as well as the more recently detected and increasingly significant lower respiratory tract viruses, such as human metapneumovirus, coronavirus, rhinovirus, and bocavirus. Congenital and neonatal forms of viral pneumonia, such as cytomegalovirus, herpes simplex virus, and measles virus, are also discussed. Postinfectious complications of viral bronchiolitis are included in this chapter due to the significant persistent morbidity during infancy in many patients.

### 17.2 Common Viruses in Infancy

Infantile respiratory viral illnesses have become an increasing cause of morbidity and mortality in populations 0–2 years of age, with approximately 300,000 pediatric hospital admissions annually in the United States and estimated hospital costs ranging from $140 to $800 million annually (Tregoning and Schwarze 2010; Coffin 2005; Hustedt and Vazquez 2010; Smuts et al. 2008). Lower respiratory tract infections (LRTI) are a leading indication for hospitalization (2–3%) in young children. Approximately 90% of LRTI in children are viral, in contrast to adults, in whom approximately 12% of community-acquired LRTIs have a viral etiology (Hammond et al. 2007; Chong et al. 2009; Welliver 2003).

The most common pathologic viruses in infancy include respiratory syncytial virus (RSV), parainfluenza virus (PIV), adenovirus (AdV), influenza virus (InfV), human metapneumovirus (hMPV), and less so coronavirus (CoV), rhinovirus (RhV), and bocavirus (BoV) (Tregoning and Schwarze 2010; Hammond et al. 2007; Chong et al. 2009). RSV remains the most prevalent and most severe of the neonatal LRTI’s (Coffin 2005; Hammond et al. 2007; Chong et al. 2009; Chang et al. 2009; Fitzgerald 2011). Studies indicate that
20–67% of children less than 1 year of age will be infected by RSV, with infection rates up to 95% by age 2 years (Tregoning and Schwarze 2010; Hammond et al. 2007; Fitzgerald 2011; Johnson et al. 2007). PIV commonly occurs within the first 6 months of life with 50% of patients affected by the first year of life (Hammond et al. 2007). Recently updated diagnostic technologies, including multiplex polymerase chain reaction (PCR) methods, have offered more accurate and faster diagnostic methods allowing appropriate treatments and patient management. Importantly, PCR for DNA viruses and reverse transcriptase PCR (RT-PCR) for RNA viruses also have allowed identification of viruses which are difficult to culture, such as hMPV and BoV, allowing better delineation of multi-agent respiratory viral infections (Tregoning and Schwarze 2010). The most common synchronously occurring respiratory viruses are RSV and RhV (Tregoning and Schwarze 2010; Chong et al. 2009; Garcia et al. 2010). In the last decade, hMPV, BoV, CoV, and RhV are increasingly recognized as causes of lower respiratory viral infections in children (Hustedt and Vazquez 2010). Relative incidence and mean age at diagnosis for infantile respiratory viral infections in the United States are summarized in Table 17.1.

Table 17.1 Infantile respiratory viruses: characteristics, relative incidence, and age at diagnosis

| Virus                      | Family        | Type | Relative incidence | Median age of diagnosis in infancy | Peak seasons            |
|----------------------------|---------------|------|--------------------|------------------------------------|-------------------------|
| Respiratory syncytial virus| Paramyxoviridae | RNA  | 56%–77%            | 4.1–10.5 months (2–3 for hospitalized infants) | Winter (Dec–Feb)        |
| Metapneumovirus            | Paramyxoviridae | RNA  | 12–28%            | 6–17.6 months (6–12 for hospitalized infants) | Winter–early spring (Dec–Apr) |
| Parainfluenza virus        | Paramyxoviridae | RNA  | 3–20%             | 15.1 months                          | Fall (Sep–Nov) – PIV1,2 Late spring–summer – PIV3 |
| Adenovirus                 | Adenoviridae  | DNA  | 1–15%             | 10.9 months                          | Fall–winter–spring (Oct–Jun) |
| Influenza virus            | Orthomyxoviridae | RNA | 1–20%             | 11.2 months                          | Fall–winter–spring (Oct–Jun) |
| Bocavirus                  | Parvoviridae  | DNA  | 4–10%             | 9.8–15 months                        | Winter (Nov–Mar)        |
| Corona virus               | Coronaviridae  | RNA  | 2–9%              | 19 months                           | Late winter–spring (Jan–Mar) |
| Rhinovirus                 | Picornaviridae | RNA  | Rare              | 4–17 months                          | Fall, spring            |
| Enterovirus                | Picornaviridae | RNA  | Rare              | No data                             | Summer, fall            |
| Epstein-Barr virus         | Herpesviridae | DNA  | Rare              | No data                             | None                    |
| Human herpes virus 6       | Herpesviridae | DNA  | Rare              | 6–12 months                         | None                    |
| Cytomegalovirus            | Herpesviridae | DNA  | Rare              | Congenital                          | None                    |
| Herpes simplex virus       | Herpesviridae | DNA  | Rare              | Congenital                          | None                    |
| Varicella zoster virus     | Herpesviridae | DNA  | No data           | May be congenital                    | None                    |
| Measles virus              | Paramyxoviridae | RNA | Rare in the United States | <12 months (unvaccinated) | Winter, spring |
| Mumps virus                | Paramyxoviridae | RNA | Rare              | <12 months (unvaccinated)          | Winter, spring          |

Welliver (2003), Williams et al. (2004), Williams (2005), Hammond et al. (2007), Smuts et al. (2008), Chong et al. (2009), Tregoning and Schwarze (2010), Hustedt and Vazquez (2010)
**17.3 Epidemiology and Risk Factors**

Known risk factors for bronchiolitis in neonates include prematurity, young age (less than 3 months), low birth weight, male gender, chronic medical conditions (congenital heart disease, chronic lung disease due to prematurity, trisomy 21, neuromuscular disorders, cystic fibrosis, gastroesophageal reflux, immunosuppression), lack of breast-feeding, preschool or school age siblings, day care enrollment, tobacco exposure, lower socioeconomic status, and crowded living conditions (Tregoning and Schwarze 2010; Coffin 2005; Hammond et al. 2007; Welliver 2003; Chang et al. 2009; Papenburg and Boivin 2010; Brodzinski and Ruddy 2009). In particular, the highest risk of mortality is associated with respiratory viral infection in premature neonates less than 1,500 g birth weight, with a reported mortality rate of 30 per 100,000 live births (Coffin 2005). The mechanisms for increased susceptibility in this population include inadequate immunologic defenses against infection, possibly due to a lack of immune experience and diminished transfer or maternal antibodies in utero, incomplete development of the neonatal airways and chest musculature, and decreased cardiopulmonary reserve due to chronic lung disease (Hammond et al. 2007; Welliver 2003; Papenburg and Boivin 2010). Chronic lung disease and congenital heart disease are both predictors of prolonged hospitalization and increased mortality due to viral bronchiolitis (Papenburg and Boivin 2010). Epidemiologic data suggests that American Indians and Alaskan Natives have a disproportionately higher mortality rate and hospitalization rate due to bronchiolitis, compared to both African Americans and Caucasians (Chang et al. 2009; Singleton et al. 2009). This higher risk in Native Americans may be due to genetic factors or due to higher prevalence of known maternal risk factors including diabetes, alcohol and tobacco usage, and delayed or absent prenatal care (Chang et al. 2009; Singleton et al. 2009).

**17.4 Disease Transmission**

Transmission of the most common LRTI viruses is typically due to exposure to infected secretions, respiratory droplets, or fomites from hands (Coffin 2005; Fitzgerald 2011). In some cases, neonatal infection by viruses such as HSV and AdV can be transmitted via vaginal delivery, with or without maternal symptoms (Hammond et al. 2007). Infectivity of the most common viruses has been correlated with seasonal variation; RSV, InfV, and hMPV are associated with winter month, whereas PIV is most common in late spring and summer months (Coffin 2005; Hammond et al. 2007; Chong et al. 2009; Garcia et al. 2010; Marcos et al. 2009; Mathisen et al. 2009).

**17.5 Clinical and Diagnostic Imaging Features**

Common clinical signs and symptoms in pediatric LRTIs include coryza, apnea, rapid shallow breaths, head bobbing, tracheal tug, chest wall hyperinflation, and intercostal retractions (Fitzgerald 2011). In addition to small airway inflammation, peripheral hyperinflation within the lung parenchyma contributes to symptoms (Tregoning and Schwarze 2010). Severe symptoms are commonly characterized by oxygen saturation less than 92–93 % (Hammond et al. 2007; Chang et al. 2009; Fitzgerald 2011; Thomson and Harris 2011). Atypical clinical presentations of viruses can be difficult to distinguish from bacterial etiologies. Typically, chest radiographs demonstrate diffuse airspace shadowing and/or dispersed areas of consolidation in bacterial pneumonia, whereas viral pneumonias more often produce hyperinflated lung parenchyma with patchy infiltrates and peribronchial cuffing (Fig. 17.1) (Coffin 2005; Chong et al. 2009). However there has been much debate about the reproducibility in the radiographic diagnosis of pneumonias, with a 48 % concordance with the WHO radiographic classification and relatively poor clinical utility in
distinguishing bacterial versus viral etiologies (Thomson and Harris 2011). One study suggests that a specific infectious agent is not identified in more than 50% of LRTIs, leaving clinicians to empirically treat with antibiotics, a potentially unnecessary drug exposure with increased risk of developing drug resistance in bacteria (Tregoning and Schwarze 2010; Marcos et al. 2009). Multiplex PCR assays have also proven very useful in LRTI diagnosis due to simultaneous detection of multiple viral agents, ability to determine viral load, and same day results in a single test (Marcos et al. 2009). IF and EIA tests have lower sensitivity (60–97%) compared to PCR techniques but are even more rapid. The simplicity of commercially available EIA kits allows their application at the bedside, yielding results within 10 min, a particularly helpful tool in peak season epidemics (Papenburg and Boivin 2010). Tissue diagnosis of respiratory viral infection is also possible via cytomorphology and immunohistochemistry (IHC); however, this requires invasive procedures, an infrequent diagnostic first step. Antibodies to viral antigens are commercially available for immunohistochemistry for most of the neonatal and infantile respiratory viruses, including RSV, PIV, hMPV, InfV, AdV, HSV, and measles virus (Hammond et al. 2007). PCR diagnosis also has been applied to formalin-fixed paraffin-embedded lung tissues (Akhtar et al. 1996). Table 17.2 compares the various diagnostic methods and their utility.

### 17.7 Histopathologic Features

The pathogenesis of symptoms related to lower respiratory tract viral infections in infants is primarily the narrowing or occlusion of conducting airways, leading to reduced gas exchange and respiratory distress (Hammond et al. 2007). A combination of direct viral injury to the epithelium and immunologic damage is responsible for pathologic changes, exacerbated by underdeveloped immunity and immature airways (Tregoning and Schwarze 2010; Coffin 2005). Histologically, respiratory viruses typically cause a pattern of lymphocytic bronchiolitis, with or without interstitial pneumonitis. Lymphocytic bronchiolitis is recognized by the presence of a circumferential cuff...
of airway-centered lymphocytes and macrophages, in some cases associated with secondary epithelial necrosis and sloughing, and plugging of bronchioles by fibrin and mucus. Squamous metaplasia of the bronchiolar epithelium and surrounding airspaces may be prominent in the healing phase of injury. Interstitial lymphocytic inflammatory infiltrates (pneumonitis) may be present, despite the fact that direct viral infection of type 1 and type 2 pneumocytes is only variably demonstrated (Coffin 2005; Hammond et al. 2007; Welliver 2003). Specific viral cytopathic effect is typically recognizable in congenital HSV and AdV infections, but viral cytopathic effect is rare or absent in most other respiratory viral infections in infants, including RSV, hMPV, PIV, and InfV. In contrast to otherwise healthy children, immunosuppressed neonates and infants (e.g., patients with bone marrow transplant, solid organ transplant, human immunodeficiency virus infection, or primary immunodeficiencies) typically have less inflammatory response and a more florid viral cytopathic effect, similar to that seen in pure culture media. Multinucleated syncytial giant cells with cytoplasmic inclusions should suggest a diagnosis of RSV, hMPV, or PIV, and immunohistochemistry or molecular testing on the tissue would be necessary for confirmation of diagnosis, if the virus has not been detected previously.

### 17.8 Specific Respiratory Viruses of Infancy

#### 17.8.1 Respiratory Syncytial Virus

RSV infection is the most common cause of both upper and lower respiratory tract infection in children, and seroprevalence approaches 100% of the population by 2 years of age (Papenburg and Boivin 2010). The peak incidence is from 6
weeks to 6 months of age (Hustedt and Vazquez 2010). Clinically, RSV infection of the upper respiratory tract causes coryza, cough, hoarseness, rhinitis, and conjunctivitis. Acute otitis media is a frequent complication. Lower respiratory tract infection due to RSV results in a syndrome of bronchiolitis (65 %) or pneumonia (21 %) and less commonly croup (11 %) or asthma exacerbation (3 %) (Williams et al. 2004). Vomiting is seen in a significant percentage of children (31 %). Hospitalization is required in 1–2 % of infected infants and mortality is relatively rare (0.02 %) but accounts for approximately 500 deaths annually in the United States (Hustedt and Vazquez 2010; Hammond et al. 2007). The histopathologic findings in RSV infection include circumferential inflammation of bronchiolar mucosa and infection of type 1 and 2 pneumocytes (Fig. 17.2) (Johnson et al. 2007). The inflammatory infiltrate consists of bronchocentric mucosal and transmural mononuclear cells (primarily T lymphocytes and

![Fig. 17.2](image)

Respiratory syncytial virus infection in an infant. The prototypic infantile respiratory virus, RSV, causes a lymphocytic bronchitis and bronchiolitis. (a) This bronchus demonstrates a cuff of lymphocytes in the submucosa (H&E, 200×). (b) Circumferential lymphocyte infiltrates are also noted in the small airways (H&E, 100×). (c) Bronchiolitis may be accompanied by an interstitial pneumonitis, characterized by interstitial widening by lymphocyte infiltrates. Syncytial-type multinucleate cells are absent or rare in lung tissues from otherwise healthy infants but are characteristic of the viral cytopathic effect seen in culture in the diagnostic virology laboratory (H&E, 100×)

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monocytes) and neutrophils. Neutrophilic infiltration centers on the bronchioles, whereas mononuclear infiltration affects both bronchioles and parenchyma. As with other viruses, airway obstruction results from epithelial and inflammatory cell debris mixed with fibrin, mucus, and edema, compounded by extrinsic compression of bronchioles by hyperplastic lymphoid follicles (Johnson et al. 2007). Syncytial giant cell formation is rare in immunocompetent children but characteristic of the histopathologic features in immunocompromised patients (Fig. 17.3) (Coffin 2005; Hammond et al. 2007; Welliver 2003).

Therapy for RSV includes use of ribavirin, a synthetic nucleoside analogue. High-risk populations of children may also be preventatively treated with palivizumab, a monoclonal antibody targeting the F protein of RSV (Papenburg and Boivin 2010).

17.9 Metapneumovirus

First identified in 2001, hMPV is now recognized to be an important and common cause of respiratory viral infection in infants, accounting for approximately 12% of all acute respiratory infections in previously healthy young children and 8–20% of culture-negative viral infections in this population (Hustedt and Vazquez 2010; Williams et al. 2004). More specifically, hMPV causes 5–15% of acute bronchiolitis in young children (Kahn 2007). Approximately 75% of hMPV infections occur in infants less than 1 year of age, and the age at diagnosis tends to be slightly older than infants with RSV infection. Seroprevalence approaches 100% of the population by 5–10 years of age, in contrast to 2 years of age for RSV (Papenburg and Boivin 2010; Brodzinski and Ruddy 2009). Most cases (75%) are diagnosed between December and April, with peak incidence in March.

Clinically, hMPV causes symptoms generally similar to RSV infection, including cough, coryza, and rhinitis in the majority of patients. Clinical diagnoses associated with hMPV include bronchiolitis (59%), croup (18%), asthma exacerbation (14%), or pneumonia (8%) (Williams et al. 2004). Acute otitis media is also common (16–50%) (Brodzinski and Ruddy 2009). Like RSV, wheezing, prolonged expiration, and hypoxemia are common features (Wolf et al. 2006). Some studies have shown less severe disease than for RSV, as indicated by shorter duration of symptoms, less frequent oxygen requirement, and less frequent respiratory support and intensive care admission (Papenburg and Boivin 2010). Hospitalization for hMPV infection is more often associated with underly-
ing medical conditions when compared to RSV infection (54 % vs. 29 %) (Williams 2005). Fatal hMPV infection has been described in immunocompromised patients (Williams 2005).

Enzyme-linked assay methods are available for rapid diagnosis of hMPV. Molecular methods (RT-PCR) are most useful for definitive diagnosis, as viral cytopathic effect is identified in culture in less than half of cases (45 %) and typically takes over 2 weeks to develop, in contrast to RSV which typically demonstrates its characteristic syncytial giant cell cytopathic effect in 3–5 days (Papenburg and Boivin 2010; Williams et al. 2004). Viral culture of hMPV also requires special conditions, including specific cell lines and trypsin supplementation (Brodzinski and Ruddy 2009). Coinfection with a second virus, such as RSV, occurs in at least 5 % of patients with hMPV and in some studies up to 30 % of hMPV infections (Brodzinski and Ruddy 2009). RSV bronchiolitis with hMPV coinfection has been suggested to produce more severe
disease, although this has not been supported in other studies (Fouchier et al. 2005).

Based on animal studies, hMPV appears to directly infect the bronchial and bronchiolar respiratory epithelium and is associated with peribronchiolar mononuclear infiltrates and intraluminal collections of mononuclear cells and neutrophils (Hammond et al. 2007). On lavage specimens, findings include respiratory epithelial cell degeneration and/or necrosis with ciliocytophthoria and round eosinophilic cytoplasmic inclusions, similar to that seen in RSV, PIV, and measles infection. A background of hemosiderin-laden macrophages, abundant neutrophils, and prominent mucus has also been noted (Hammond et al. 2007; Vargas et al. 2004). Acute and organizing lung injury (diffuse alveolar damage) has been reported (Papenburg and Boivin 2010). There is no currently approved vaccine or specific antiviral therapy for hMPV.

17.10 Parainfluenza Virus

Clinically, PIV causes a clinical syndrome of croup (laryngotracheitis) in the majority of patients (64 %). Less common manifestations include bronchiolitis (28 %), pneumonia (7 %), and asthma exacerbation (2 %) (Williams et al. 2004). There are four serotypes of parainfluenza virus: PIV1, PIV2, PIV3, and PIV4. PIV1 and PIV2 are seasonal with highest prevalence in the fall months in the United States, whereas PIV3 occurs year-round with peak in the late spring and summer. PIV3 bronchiolitis and pneumonia are typically seen in young infants, less than 6 months of age, whereas PIV1 and PIV2 more often cause upper respiratory tract disease in toddlers and young children (2–5 years of age). PIV4 is often asymptomatic and infrequently detected. Mortality for PIV is quite low, except for overwhelming infection in immunocompromised patients. Histopathologic features in the general population are not well described, but animal models of PIV infection demonstrate infection of the bronchiolar epithelium, bronchiolitis, and pneumonitis (Hammond et al. 2007). Histologically, PIV produces a giant cell pneumonia and occasional cytoplasmic inclusions in the immunocompromised host, histologically indistinguishable from RSV or metapneumovirus infection (Fig. 17.4).

17.11 Adenovirus

Clinically, adenovirus is associated with several different syndromes, including keratoconjunctivitis, gastroenteritis with diarrhea, cystitis, and respiratory tract disease. In the respiratory tract, adenovirus is associated most often with bronchiolitis (61 %) or croup symptoms (21 %) and less often pneumonia (14 %) or asthma exacerbation (4 %) (Williams et al. 2004). Community-acquired infections are spread by respiratory droplets, although neonatal infection may follow vaginal delivery in infected mothers, often associated with prolonged rupture of membranes (Hammond et al. 2007).

Severe AdV infections cause necrosis and destruction of bronchial and bronchiolar epithelium, as well as adjacent parenchymal necrosis. Parenchymal necrosis may be widespread in immunocompromised patients, and AdV carries a particularly high mortality in this population due to disseminated disease. Within the respiratory and alveolar-type epithelium, nuclear inclusions appear as diffuse amphophilic material with peripheralization of chromatin (“smudge cells”) or less commonly as eosinophilic central nuclear inclusions with a peripheral halo, similar to that seen in Cowdry A herpes simplex virus inclusions (Hammond et al. 2007). Postinfectious obliterative bronchiolitis (bronchiolitis obliterans syndrome) is a common sequela in neonates and immunocompromised patients due to the severity of bronchiolar mucosal necrosis caused by adenovirus.

17.12 Influenza Virus

Influenza virus clinically may cause fever (87 %), vomiting (28 %), conjunctivitis (22 %), croup symptoms (41 %), bronchiolitis (22 %), or pneumonia (28 %) (Williams et al. 2004).
In contrast to hMPV, asthma exacerbation is not a typical feature of InfV infection. InfV occurs in individuals across a broad age range during periods of regional epidemics or occasionally as part of a major global pandemic, as in the influenza outbreaks of 1918, 1957, and 1968. The peak incidence is in the winter months in the United States and may induce severe disease in young infants, the elderly, and immunocompromised populations. The virus primarily infects the bronchial and bronchiolar respiratory epithelium, but occasional alveolar epithelial cells can also be demonstrated by immunohistochemistry. Classically, InfV infection produces a necrotizing bronchiolitis, peribronchiolar infiltrates, interstitial inflammation, pulmonary edema, and hyaline membranes (diffuse alveolar damage) (Fig. 17.5). Secondary bacterial pneumonia is common in fatal cases (47 %) (Bhat et al. 2005; Guarner et al. 2006). There are currently four antivirals effective against InfV infection: amantidine, rimantadine, anamivir, and oseltamivir. Vaccination is recommended for infants greater than 6 months.
old and for pregnant women for protection of their neonates in the first 6 months of life by passive immunity.

### 17.13 Bocavirus

Bocavirus is a recently identified viral agent of the pediatric airway, discovered in 2005. It is identified in approximately 5% of previously undiagnosed respiratory viral infections in children. By seroprevalence studies, almost all children are exposed to BoV by 5 years of age and the average age at diagnosis is 13–15 months (Hustedt and Vazquez 2010). The true role of BoV as a causative agent of respiratory infection has been controversial due to high rates of viral coinfection (Milder and Arnold 2009). hMPV and/or BoV are identified in about half of viral coinfections in children (Hustedt and Vazquez 2010). Nevertheless, most available studies with controls have shown few or no asymptomatic patients detected with BoV, lending credence that BoV is a true pathogen in children (Brieu et al. 2008). Similar to other pediatric respiratory viral infections, symptoms of BoV include fever, rhinorrhea, cough, sore throat, and wheezing. Furthermore, BoV has been identified in some patients with gastroenteritis (1–9%) and as a potential cause of Kawasaki disease (31%) (Brodzinski and Ruddy 2009). Peak incidence of BoV is in the winter months, similar to RSV and hMPV. Laboratory diagnosis can be made by EIA method or PCR technology. The mainstay of treatment is supportive care, and there are no available medical therapies at this time.

### 17.14 Coronavirus

Coronaviruses have long been appreciated as a significant cause of mild upper respiratory tract infections (CoV types OC43 and 229E), but only relatively recently have been appreciated as an occasional cause of lower respiratory tract infections in children (Canducci et al. 2008). Following the severe acute respiratory syndrome (SARS) epidemic in 2003, increased attention to the corona- viridae family of viruses revealed a new variant discovered in the Netherlands in 2004 (hCoV NL63) and another variant discovered in Hong Kong in 2005 (hCoV HKU1), both causing pediatric bronchiolitis and pneumonia (Brodzinski and Ruddy 2009). CoV NL63 has been detected in approximately 2–9% of upper and lower respiratory tract infections in children and approximately 2.5% of specimens from young children with viral illness with acute wheezing (Smuts et al. 2008). CoV is difficult to isolate in cell culture, and molecular methods are most often used
for laboratory detection (Kahn 2007). CoV is identified year-round, although seasonal peaks have been described from January to March (Smuts et al. 2008; Brodzinski and Ruddy 2009).

### 17.15 Rhinovirus

Rhinovirus is a picornavirus that is most often recognized as a cause of the common “cold” (rhinitis) but is increasingly recognized as a cause of lower respiratory tract viral infections at all ages based upon molecular detection methods (Atmar et al. 2012). In infants, the peak ages of infection are reported from 4 to 17 months. Peak seasons are in the fall and spring.

### 17.16 Cytomegalovirus

In fetuses and neonates, cytomegalovirus infection may be acquired vertically during pregnancy. CMV infection also may be latent and emerges as an opportunistic infection in immunocompromised patients. In immunocompromised patients, clinical diagnosis of CMV pneumonia requires not only detection of the virus in a respiratory sample but also presence of respiratory symptomatology. Congenital CMV infection manifests as disseminated disease with frequent viral cytopathic effect, classically inducing cytomegaly, large intranuclear inclusions with a peripheral halo, and small granular basophilic cytoplasmic inclusions. CMV pneumonitis may be associated with lymphoplasmacytic inflammation in the alveolar walls.

### 17.17 Herpes Simplex Virus

Herpes simplex virus pneumonia typically occurs as a congenital infection in newborns. It is most often acquired from infected cervicovaginal secretions during vaginal delivery, followed by a typical incubation period of 9–10 days before skin lesions or liver failure are detected. Alternatively, neonatal infection may be acquired from infected oral secretions of parents or other caregivers. Intrauterine infection from maternal viremia is rare. Clinical presentation is typically unsuspected and fulminant, requiring rapid diagnosis and treatment. Mortality is high in the setting of disseminated disease (57 %), and the morbidity in surviving neonates following encephalitis may include seizures, spasticity, blindness, and learning disabilities. Congenital HSV infection is regrettably difficult to predict and prevent, as herpetic vesicles may not be apparent in infected mothers. The histologic features, regardless of organ involved, are characterized by punctate areas of necrosis surrounded by a rim of cells with characteristic intranuclear viral cytopathic effect (Cowdry A or Cowdry B type inclusions) (Fig. 17.6).

### 17.18 Measles Virus

Measles virus pneumonia is now rare in the United States due to vaccination programs but is common in developing countries. Young infants who have not yet had scheduled vaccinations are susceptible to primary infection and are at the greatest risk for severe or fatal disease (Hammond et al. 2007). In immunocompromised hosts, measles virus infection classically results in a giant cell pneumonitis composed of an interstitial pneumonia with large multinucleate syncytial giant cells lining the airspaces. Some giant cells may have intracytoplasmic globular eosinophilic inclusions, reflecting aggregates of cytoplasmic RNA virus. Diffuse alveolar damage and squamous metaplasia are variable features (Radoycich et al. 1992). In immunocompetent children, necrotizing bronchiolitis is noted, but giant cells are typically sparse, and cytoplasmic inclusions are not apparent (Radoycich et al. 1992).

### 17.19 Complications of Infantile Viral Infection

Postinfectious reactive airway disease/asthma. Following acute infection, viruses can cause chronic sequelae, such as postinfectious recurrent wheezing in 40–50 % of RSV, hMPV, and
RhV patients. Severe RSV bronchiolitis is associated with an increased risk of hospitalization for asthma in the short term (Papenburg and Boivin 2010). Some suggest that greater severity of RSV bronchiolitis may reflect an intrinsic genetic predisposition for asthma. hMPV is detected in approximately 8–9% of children with recurrent wheezing and BoV in approximately 5–6% (Smuts et al. 2008). Specifically, hMPV bronchiolitis carries a fivefold risk of future development of asthma compared to control patients hospitalized for gastroenteritis (Brodzinski and Ruddy 2009).

Postinfectious bronchiolitis obliterans syndrome. Obliterative bronchiolitis and bronchiectasis may follow any form of necrotizing bronchiolitis but is most often reported as a sequel of AdV infections (Tregoning and Schwarze 2010; Coffin 2005; Hammond et al. 2007; Chong et al. 2009; Garcia et al. 2010; Chang et al. 2009). Clinically, postinfectious bronchiolitis obliterans syndrome is character-
ized by obstructive pulmonary function tests and chest CT evidence of bronchiectasis and regional air trapping (“mosaic perfusion”) best seen on expiratory images. Histologically, obliterative bronchiolitis is characterized by fibrous obliteration or constriction of small airways by subepithelial fibrosis (Fig. 17.7). This finding may be subtle and subject to sampling error on wedge lung biopsy, and connective tissue stains such as trichrome or Movat pentachrome are helpful in eliciting the fibrotic airways within bronchovascular bundles.

17.20 Summary

Respiratory viral infection in infants differs from that seen in adults. Neonates and infants are predisposed to RSV, hMPV, and PIV, in contrast to RhV, CoV, and InIV, the most common lower

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**Fig. 17.7** Complications of infantile respiratory viral infection. (a) Following acute necrotizing respiratory viral infection, the bronchioles may develop mucosal reparative changes in the form of squamous metaplasia, in this case following parainfluenza virus (H&E, 100×). (b) In this case, also following parainfluenza virus infection, the bronchioles demonstrate focal constrictive subepithelial fibrosis (constrictive bronchiolitis), part of the spectrum of pathologic features associated with post-viral bronchiolitis obliterans syndrome (H&E, 200×). This is a common complication of both adenovirus and influenza virus bronchiolitis
respiratory tract viruses in adults. Premature infants are particularly susceptible to these viral infections and carry a higher morbidity and mortality relative to the adult population. Laboratory diagnosis by viral culture, EIA, IF, and multiplex PCR assays are the mainstays of specific diagnosis in infancy, similar to older children and adults. Despite the increasingly recognized prevalence of culture-negative respiratory viruses such as hMPV, BoV, and CoV, RSV remains a central pathogen in respiratory infections in infants and tends to be more severe than these other viruses. Pathologic features in lung biopsy or autopsy vary dependent on the immunologic status of the patient. Immunocompromised infants have more pronounced viral cytopathic effect (giant cells and/or viral inclusions) and relatively little inflammatory response, whereas otherwise healthy infants more often have lymphocytic bronchiolitis or pneumonitis without distinguishing viral cytopathic effect. Immunohistochemistry may be used for confirmation of diagnosis in tissues; however, the more cost-effective and comprehensive method for confirmation of diagnosis currently is the use of molecular diagnostic techniques.

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