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156 Parainfluenza Viruses

Michael G. Ison

SHORT VIEW SUMMARY

Definition
- Parainfluenza virus (PIV) causes acute respiratory illness, including colds, croup, bronchiolitis, and pneumonia.

Epidemiology
- PIV-1 and PIV-2 cause seasonal outbreaks in the fall, with PIV-1 causing epidemics in odd-numbered years. Clinically, PIV-1 is strongly associated with croup in children.
- PIV-3 causes annual epidemics in the spring; in years in which PIV-1 does not circulate, the season is typically more active and prolonged. PIV-3 is associated with more severe infections, particularly among immunocompromised adults and children.
- PIV-4 is associated with milder disease, typically limited to the upper airway.
- Although antibodies are produced in response to clinical disease, reinfection is common throughout life.
- Disease, particularly associated with PIV-3, frequently progresses to the lower airway in immunocompromised adults and children and is associated with significant morbidity and mortality.

Microbiology
- PIV is a single-stranded, enveloped RNA virus belonging to the Paramyxoviridae family. It includes PIV-1, PIV-2, PIV-3, and PIV-4.

Diagnosis
- National PIV trends are available at https://www.cdc.gov/surveillance/nrevss/human-paraflu/index.html.
- Laboratory diagnosis can be made through culture or polymerase chain reaction (PCR) assay, with improved sensitivity with molecular diagnostic methods.

Therapy
- Croup is generally treated with glucocorticoids and nebulized epinephrine in young children.
- Although ribavirin and intravenous immunoglobulin have been used in the treatment of immunocompromised adults and children, their efficacy is uncertain.
- A number of novel antivirals are currently under development.

Prevention
- Standard and contact precautions are recommended to avoid nosocomial spread of PIV in the health care setting.
- A number of live-attenuated vaccine candidates are undergoing development.

Parainfluenza viruses (PIVs) are paramyxoviruses that are important causes of respiratory viral infections in adults and children. Although parainfluenza is a leading cause of croup in children, broader use of molecular diagnostics has refined our understanding of the impact of PIV on adults and children.[1] Infection is typically mild and self-limited, but life-threatening lower respiratory tract infections do occur, particularly in immunocompromised or elderly patients.[1–3]

VIROLOGY

PIVs are single-stranded, enveloped RNA viruses belonging to the Paramyxoviridae family (Fig. 156.1).[4,5] There are four major serotypes of human PIV (PIV-1, PIV-2, PIV-3, PIV-4), which are defined by complement fixation and hemagglutinating antigens.[1,6,7] PIV-1 and PIV-3 are members of the genus *Respirovirus,* whereas PIV-2 and PIV-4 are members of the genus *Rubulavirus.* Although the hemagglutinin-neuraminidase (HN) glycoproteins of PIV are more antigenically stable than those of influenza A viruses, antigenic differences have been reported over time.[8]

The virions are pleomorphic, range in diameter from 150 to 200 nm, and have a lipid bilayer envelope derived from the host cell.[7] The single strand of negative-sense RNA encodes at least six viral proteins: the nucleocapsid protein (NP), the phosphoprotein (P), the matrix protein (M), the fusion glycoprotein (F), the HN glycoprotein, and the RNA polymerase (L).[9] The HN and F proteins sit in the lipid envelope and form the major antigenic targets for neutralizing antibody.[10] The nucleocapsid core is composed of NP, P, and L proteins in association with viral RNA. NP proteins bind tightly to the viral genome, creating a template for the RNA-dependent RNA polymerase composed of the P and L proteins.[11] The HN glycoproteins are critical to attachment of the virus to the host cell wall at sialic acid residues on the cell surface.[12] Once attached to the cell, the F protein mediates virus–cell membrane fusion and subsequent infection of the host cell. The neuraminidase portion of the HN protein cleaves the progeny virions free from the surface of an infected cell.[12,13]

In addition to these essential proteins, each PIV expresses nonessential proteins: PIV-1 and PIV-3 RNA encode short C proteins, PIV-2 RNA encodes a V protein, and PIV-3 also expresses a D protein. Although the function of the D protein is unknown, the C and V proteins suppress the activity of type 1 interferons and likely play a role in the pathogenesis of disease.[14,15]

Viral replication takes place in the cytoplasm, where the NP protein assembles with the genomic RNA to form a helical structure. This NP-RNA complex is then joined by the P and L protein complexes to form the nucleocapsid. The envelope proteins are assembled preferentially on the apical surface of the cell. Finally, the matrix plays a role in the final assembly of the virus and subsequent release from the cell by budding. The neuraminidase activity of the HN is critical in facilitating release from the cell and preventing virus clumping.

PATHOGENESIS

PIVs preferentially infect ciliated epithelial cells that line the upper and lower respiratory tracts.[16] After exposure, replication begins in the epithelial cells of the nose and oropharynx with subsequent spread to the large and small airways.[17] Although replication can be first recognized about 24 hours after infection, peak replication occurs 2 to 5 days after infection.[18] Shedding typically begins to decrease after 7 days.[19] The extent of infection correlates well with disease; mild upper respiratory infections are associated with limited infection of the nasopharynx,

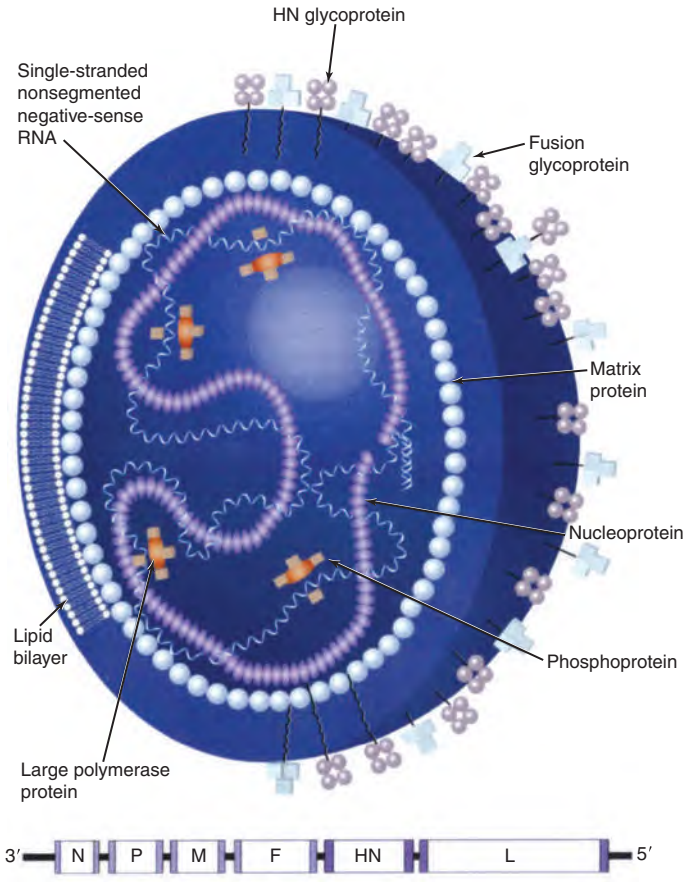

FIG. 156.1 Human parainfluenza virus virion and genome organization. *F,* Fusion; *HN,* hemagglutinin-neuraminidase; *L,* large; *M,* matrix; *N,* nucleocapsid; *P,* phosphoprotein. *(Modified from Schmidt AC, Schaap-Nutt A, Bartlett EJ, et al. Progress in the development of human parainfluenza virus vaccines.* Expert Rev Respir Med. *2011;5:515–526.)*

whereas more severe disease is generally associated with replication in the large and small airways.[20,21] Peak symptoms correlate with peak viral replication. Infection of the larynx and upper trachea is associated with croup, whereas bronchiolitis and pneumonia are associated with infection of the distal airways.[18]

Animal models of infection suggest that there is limited damage to infected cells because of direct viral effects.[19] Instead, the host immune response appears to play an important role in the pathogenesis of PIV infection.[18] Specifically, the key host immune responses that contribute to viral clearance, including the innate immune responses, $CD8^+$ and $CD4^+$ T-cell responses, interferon production, and local and systemic immunoglobulin A (IgA), IgE, and IgG responses, are also the key drivers of the clinical signs and symptoms of infection.[18] Stromal interleukin-11 production, enhanced acetylcholine release, and increased release of leukotrienes induced by PIV-3 infection, for example, appear to be associated with increased airway responsiveness during infection.[22–24]

There are two major components of the immune response to PIV: humoral and cellular immune responses. Both serum neutralizing antibodies and T-cell recognition are directed at the HN and F surface proteins of PIV.[7] Although there is a slight degree of antigenic variability in these proteins, reinfection appears to generally result from waning immunity instead of significant drift of antigenic epitopes.[25] Mucosal IgA immunity appears to be more important than systemic IgG-derived immunity in the prevention of infection.[7] Once PIV replication is ongoing, cytotoxic T cells play a critical role in the control and clearance of PIV infection. Lack of this cellular immune response is associated with progressive disease, as is demonstrated by the increased risk of progressive and fatal disease in hematopoietic stem cell transplant (HSCT) recipients.[26] Recently, the cellular immune response to PIV has been more carefully characterized.[27] Both $CD4^+$ and $CD8^+$ T cells were found to be capable of producing Th1-polarized effector cytokines and killing PIV3-expressing targets. The potential impact of this response was suggested by correlation between the presence of PIV3-specific T cells and viral control in allogeneic HSCT recipients.[27]

EPIDEMIOLOGY

PIVs are transmitted by direct person-to-person contact through large respiratory droplets and contact with fomites contaminated with respiratory secretions.[28] After initial exposure to the virus, clinical symptoms typically develop after a 2- to 6-day incubation period. Initial infection with parainfluenza typically occurs early in childhood, most commonly in children younger than 5 years. Serologic studies have demonstrated that PIV-3 affects up to 50% of children within the first year of life, with PIV-1 and PIV-2 causing initial infections later, generally between ages 3 and 5 years.[29,30] By adulthood, more than 90% of humans have antibodies to PIV.

The burden of PIV infection has been recognized to be more significant in children historically. In fact, PIV is responsible for 20% to 40% of lower respiratory tract infections in children. Parainfluenza is the second most common viral cause of hospitalization in children.[31] Hospitalization is required in 2.8 per 1000 children according to one report and is associated with 7600 to 48,000 pediatric hospitalizations annually in the United States.[32] Rates of hospitalization are higher in children younger than 1 year (1.9–12 per 1000 children) than in children aged 1 to 4 years (0.5–2 per 1000 children).[33] PIV-3 causes most infections necessitating hospitalization in children.[30,33] A recent study demonstrated that PIV was a common cause of hospitalization in children with pneumonia, with a rate similar to that of influenza.[34] With the advent of more contemporary assays, the impact of PIV in adults has also been appreciated.[2] In one recent study, PIV-3 was the third most commonly isolated viral isolate in individuals 16 to 64 years old who required hospitalization (0.7 per 1000 population).[35] In adults presenting with an influenza-like illness during the 2009 influenza pandemic, PIV-3 was the second most common cause of illness after influenza in adults.[36] Among adults hospitalized with pneumonia, PIV was a commonly identified pathogen, with about half the rate of influenza and a similar rate to respiratory syncytial virus (RSV).[37] In both adults and children, reinfection is common despite the presence of antibodies formed during prior infection.[38] Reinfection is typically associated with milder disease than initial infection and is typically limited to the upper airway.[38]

PIV-3 is the most prevalent serotype and is associated with pneumonia and bronchiolitis. PIV-1 and to a lesser extent PIV-2 are associated with croup in children. PIV-1 and PIV-2 are seen less frequently in adults and can be associated mostly with upper respiratory tract infection, although lower respiratory tract disease has also been described.[2,7,26,39] In adults hospitalized with pneumonia, PIV-3 was found in 3.1% of patients, PIV-1 in 2.5%, and PIV-2 in 0.2%.[40] PIV-4 causes only mild upper respiratory tract infection in both adults and children.

Although PIV-1, PIV-2, PIV-3, and PIV-4 cause disease in all parts of the world, the seasonal patterns of PIV infections depend on the specific locations. In tropical and subtropical regions, PIVs do not show seasonal variations.[41] In the United States, PIV-1 and PIV-2 cause seasonal outbreaks in the fall (September through December); of interest, PIV-1 epidemics occur every other year, typically in odd-numbered years (Fig. 156.2).[42] PIV-3 causes epidemics during the spring (April through June). In years when there is no PIV-1 circulating, PIV-3 activity is generally higher, with either a longer spring season or a small second period of increased activity in the fall.[42] There are fewer data available on PIV-4, in part because of the generally mild degree of illness caused by the virus. It appears that PIV-4 is more common in the autumn and winter months.[43]

In addition to age and geography, other factors may affect the presentation and severity of illness caused by PIV. Sex and ethnicity may play a role in the severity of PIV infection because PIV-associated bronchiolitis occurs most commonly in nonwhite males.[21] Breastfed infants have a reduced risk of severe infection with PIV. Pneumococcal vaccination is associated with a reduced risk of pneumonia in infants with PIV.[44] Last, patients with immune compromise may shed PIV for prolonged

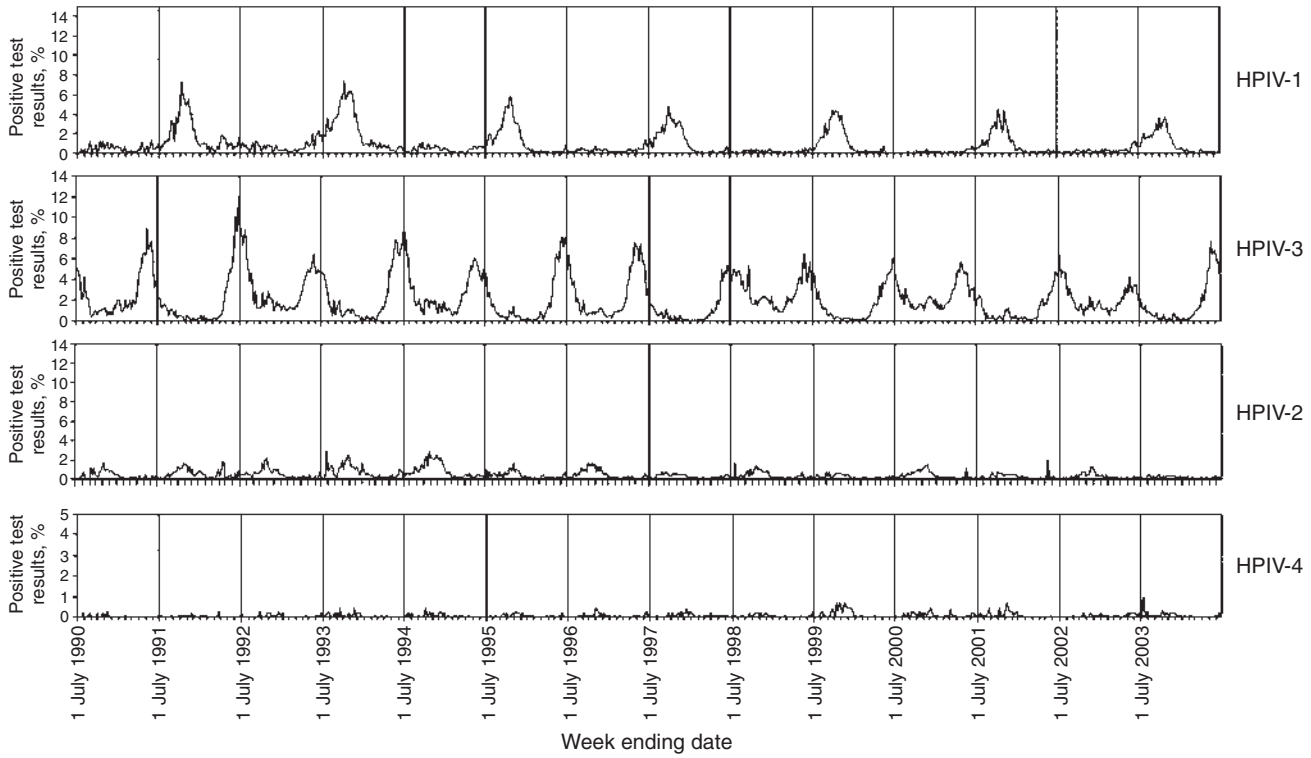

FIG. 156.2 Seasonal distribution of human parainfluenza virus *(HPIV)* serotypes 1, 3, 2, and 4 from July 1990 to June 2004. The percentage of tests positive for HPIV serotypes 1, 3, 2, and 4 reported to the National Respiratory and Enteric Virus Surveillance System in the United States, by week, July 1990 to June 2004. Note that HPIV-4 has different axis scales than the other HPIV serotypes. *(Modified from Fry AM, Curns AT, Harbour K, et al. Seasonal trends of human parainfluenza viral infections: United States, 1990–2004.* Clin Infect Dis. *2006;43:1016–1022.)*

periods of time, and infections may be associated with increased risk of progression to the lower airway and fatal outcomes. Parainfluenza is one of the more common causes of respiratory viral infections in patients with hematologic malignancies, HSCT, or solid-organ transplantation and is associated with a high rate of progressive disease involving the lower airway and an increased mortality rate.[26,45]

CLINICAL MANIFESTATIONS

PIVs cause a variety of upper and lower respiratory tract illnesses, ranging from mild coldlike syndromes to life-threatening pneumonias. Although PIV infection may require hospitalization, most infections are mild and self-limited and can be managed on an outpatient basis.

Pediatric Disease

Most infections in children are limited to the upper respiratory tract, with only about 15% involving the lower respiratory tract.[46] Upper respiratory tract disease is associated with otitis media and sinusitis in 30% to 50% of children and less frequently in adults; this complication can result from primary viral infection or secondary bacterial superinfection.[46–48] Although no one particular virus is associated with a classic clinical presentation, specific PIV serotypes are more strongly associated with certain clinical presentations. PIV-1 and PIV-2 are associated with croup, or laryngotracheobronchitis, in children.[1,49] PIV-induced croup generally manifests with fever, rhinorrhea, and pharyngitis, which is typically followed by a barking cough associated with stridor, dyspnea, and chest wall retractions.[1,49] Hospitalization for respiratory distress and hypoxemia occurs, particularly if there is significant involvement in the lower airway.[30] Disease caused by PIV-2 is generally less severe than that caused by PIV-1. Alternatively, PIV-3 is associated with more distal lung involvement, particularly in the first 6 months of life.[1,50] PIV-3 pneumonia and bronchiolitis in children are clinically difficult to differentiate from RSV infection. PIV-4 is generally associated with mild upper respiratory infections or asymptomatic infection. Rarely, particularly in children with underlying cardiopulmonary disease or immune compromise, more severe infections can occur because of PIV-4.[1,51]

Although PIV infection is generally limited to the respiratory tract, nonrespiratory complications, including meningitis, myocarditis, pericarditis, and Guillain-Barré syndrome, have been described in adults and children.[52–55]

Adult Disease

PIV infections in immunocompetent adults are usually asymptomatic or mild, self-limited upper respiratory tract infections.[2,56] PIV is responsible for 1% to 15% of acute respiratory illnesses in adults, with higher rates and more significant morbidity in older adults.[39] Up to 11% of elderly patients developed PIV pneumonia in one study, whereas up to 14% of nursing home residents developed respiratory illness attributable to PIV.[57,58] Fatal cases and outbreaks in long-term care facilities have been described.[39] With the wider use of more sensitive molecular assays, PIV has been demonstrated to be a significant cause of community-acquired pneumonia.[2,37,59–61] PIV is also increasingly associated with exacerbations of asthma and chronic bronchitis.[2,24,62–64]

In general, PIV-3 is associated with a higher risk of lower tract disease in adults, and PIV-4 is usually associated with milder upper respiratory tract disease. PIV-1 and PIV-2 have a broader spectrum of disease in adults, with a risk of lower respiratory tract disease between that of PIV-3 and PIV-4. Most adults present with fever, rhinorrhea, cough, and a sore throat that does not clinically distinguish it from other respiratory viruses.[2,39]

Parainfluenza Virus in Immunocompromised Patients

PIV causes significant direct and indirect morbidity and mortality among immunocompromised adults and children.[65,66] Most studies conducted to date have focused on patients admitted to the hospital, and as a result, data may underestimate the incidence and overestimate the severity of disease caused by PIV. Among HSCT recipients, the incidence of PIV is 4% to 7%, of which 13% to 43% have lower respiratory tract involvement.[45] Mortality ranges from 12% to 50%, with enhanced mortality in patients with lower respiratory tract disease and earlier

onset after transplant.[3,45,67,68,69–72] Although nosocomial outbreaks have been described, most cases appear to be community acquired, with PIV-3 being the most frequent type to cause disease.[69,73–75] PIV is associated with asymptomatic shedding among HSCT recipients and may contribute to the risk of nosocomial spread when only symptomatic patients are tested and isolated.[3]

At presentation, most HSCT recipients present with upper respiratory tract–only involvement (57%–87%), and 13% of patients with upper respiratory tract disease will progress to lower respiratory tract disease, usually within 1 week.[26,67,76,77] Steroids, in a dose-dependent manner, are associated with increased risk of progression from upper to lower respiratory tract disease and mortality.[69,77,78] Other risk factors for progressive disease include early onset after transplant, allogeneic (matched unrelated and matched related) donor, presence of lymphocytopenia, active graft-versus-host disease, and pediatric age group.[26,45,76,78] Reduced-intensity conditioning appears to be a risk factor for late-onset (≥30 days) PIV infection.[76] Mortality, even with treatment, in patients with lower airway disease remains high.[76,77] Copathogens are frequently found in patients with PIV and may contribute to the significant morbidity and mortality of infection.[79] In addition to the morbidity and mortality directly attributed to PIV infection, PIV infection is associated with 17.9-times-greater odds of developing severe airflow declines after infection.[80] This progressive decline in pulmonary function is associated with functional impairment and increased morbidity and mortality.

Parainfluenza has also been demonstrated to cause severe disease in patients undergoing chemotherapy.[81,82] Risk appears highest in children and patients being treated for hematologic malignancies.[82,83] In general, infection is acquired in the community and more frequently affects children younger than 2 years and those with acute lymphoblastic leukemia.[82] Lymphocytopenia appears to be a risk factor for lower airway disease; despite causing significant morbidity, it is infrequently fatal.[82] Children with severe combined immunodeficiency undergoing HSCT have developed a rapidly fatal giant cell pneumonia caused by PIV.[84]

A wide range of imaging findings, including interstitial infiltrates, ground-glass opacities, and/or airspace consolidations, have been demonstrated in HSCT patients with PIV pneumonia.[26] Rarely, small peribronchial nodules have been described, suggesting that PIV must be included in the differential diagnosis of nodular pneumonia in immunosuppressed patients.[85] Because these findings are not specific for PIV, appropriate studies should be done to rule out alternative pathogens, including bacterial and fungal pathogens that often complicate PIV infections in these patients.

Data on the impact of PIV on solid-organ transplant recipients are more limited, with most data coming from lung transplant recipients.[26,86,87] The incidence of PIV in lung transplant recipients is about 5%.[88,89] PIV infections among lung transplant recipients have been associated with significant short- and long-term pulmonary dysfunction. Animal models of a related virus (Sendai) have suggested that there is a complex interplay between direct viral cytopathic effects and local induction of inflammation that contributes to allograft rejection.[90,91] Although PIV may cause acute rejection, the pathologic picture could also be associated with immunologic response to viral infection, which makes interpretation of biopsy findings challenging.[88,92] There are more convincing data from lung transplant recipients that PIV, particularly with lower respiratory tract infection, is associated with development or progression of bronchiolitis obliterans or bronchiolitis obliterans syndrome.[87,88,89,92,93]

DIAGNOSIS

Local surveillance for PIV is not routinely available in most parts of the United States. National trends are monitored and available as part of the National Respiratory and Enteric Virus Surveillance System (https://www.cdc.gov/surveillance/nrevss/human-paraflu/index.html).

PIV can be diagnosed through culture, antigen detection, or nucleic acid testing. Swabs, aspirates, and washes from the nasopharynx or oropharyngeal secretions are appropriate specimens for making a diagnosis, with paired oropharyngeal and nasopharyngeal samples associated with the highest sensitivity. For patients with pneumonia or in whom lower airway involvement is suspected, bronchoalveolar lavage fluid may be used for diagnosis of PIV and may increase diagnostic yield. PIV is stable in viral transport medium at 4°C for up to 5 days. Freezing to −20°C does decrease infectivity of the virus, but long-term storage can be achieved easily by adding sucrose or glycerol to the holding media and freezing to below −70°C.[6] Historically, cell culture was considered the gold standard for the diagnosis of PIV. PIV is culturable on LLC-MK2 rhesus monkey kidney, Vero African green monkey kidney, and NCI-H292 human lung carcinoma cell lines with use of standard and shell vial techniques[7]; fixed-mixed cell lines, such as R-Mix (Diagnostic Hybrids, Athens, OH), have sensitivity that approaches that of standard cell culture lines for the detection of PIV and are more broadly used in many clinical laboratories currently.[6,94–96] Trypsin is required for the growth of PIV-1 and PIV-4 but not PIV-2 and PIV-3.[7] Hemadsorption-inhibition, hemagglutination inhibition, or immunofluorescence is used to identify the PIV in cultures.[6]

With broader availability and improved sensitivity, polymerase chain reaction (PCR)–based tests are now considered the gold standard for the diagnosis of PIV. Typically, these are directed toward the HN gene, although exact primers have differed among assays. Several studies have demonstrated the improved sensitivity of PCR-based assays over cultures for the diagnosis of PIV, particularly in immunocompromised patients.[97,98–100] Yield of detection may be increased by 1.5-fold or higher, compared with culture, for PCR systems in the diagnosis of PIV.[99] Because no one clinical syndrome is associated with a unique virus, assays that simultaneously detect multiple viruses are considered best for diagnosis. Despite the advantages of highly multiplexed PCR-based systems in detecting a wide range of viruses, the diagnostic yield for PIV is not consistent for all available systems.[101–103]

There are currently no approved rapid antigen kits available for the detection of PIV. There are several monoclonal antibody systems that allow identification and differentiation of the different PIV serotypes in primary patient samples and from cell cultures.[6,104]

THERAPY

There are currently no antivirals with proven efficacy that are approved for the treatment of PIV infections. For children with croup, glucocorticoids and nebulized epinephrine have been associated with improved clinical outcomes.[105,106] Glucocorticoids, generally dexamethasone and budesonide, are associated with improved Westley scores at 6 and 12 hours after administration, in addition to fewer clinic visits and admissions for croup.[106] Furthermore, glucocorticoids are associated with shorter emergency room and hospital visits and reduced use of nebulized epinephrine.[106] Use of nebulized epinephrine is associated with improvement in croup scores at 30 minutes but not at 2 and 6 hours after treatment, and also with shorter hospital stays compared with placebo.[105] There is generally no difference in early responses when racemic epinephrine is compared with L-epinephrine nebulization.[105]

Of the available data regarding the use of antiviral agents for treatment of PIV, many come from immunocompromised patients. The mainstay of therapy in these patients is reduction of immune suppression, particularly steroids, if possible.[65,66] Most publications have been case reports or small case series of HSCT and solid-organ transplant patients who have received aerosolized, oral, or intravenous ribavirin for the treatment of PIV.[a] In the largest study published, 31 of 55 PIV-infected HSCT recipients received aerosolized ribavirin with or without intravenous immunoglobulin. In this study, treatment was not associated with reduction in viral shedding or mortality.[69]

A number of antiviral agents with activity against PIV are currently being tested. (Also see Chapter 45.) Two HN inhibitors (BCX 2798 and BCX 2855) have been developed and have potent in vitro and in vivo activity against PIV; there are no human data yet on these novel inhibitors.[115,116] DAS181 is a novel antiviral agent that consists of a sialidase from *Actinomyces viscosus* attached to a respiratory epithelium anchoring domain.[117] The drug cleaves the terminal sialic acid residues from the surface of human respiratory epithelial cells, thereby reducing binding and therefore infectivity of PIVs.[117] DAS181 has been used in lung and stem cell transplant patients, with documented PIV-3 infection derived from clinical and radiologic evidence of lower airway involvement.[2,118–125] Although not all patients had improvement in symptoms, oxygenation, pulmonary function, and nasopharyngeal viral loads, those without

[a]References 2, 45, 55, 68–71, 76, 88, 107–114.

coinfections tended to have the best response to therapy.[2] Favipiravir, a pyrazine derivative that has antiviral activity against multiple RNA viruses, including paramyxoviruses, has been shown to have in vitro activity against PIV-3 in tissue culture (90% effective concentration [EC_{90}] of 36 μM).[126]

Preclinical data show promise for immunoglobulin and short interfering RNAs (siRNAs) for the treatment of PIV,[127] although there are currently no data in humans to prove efficacy of either of these interventions. Human PIV immunoglobulin and convalescent rat serum were associated with reduced PIV titers when delivered to rats intranasally.[128] Likewise, to date, siRNAs prevented infection in mice in one study.[129]

PREVENTION

Despite the significant clinical impact of PIVs, there is currently no licensed vaccine. Although natural immunity to PIV allows reinfection, subsequent infections are typically milder in nature.[5] Natural infection results in antibody development to all viral proteins, but the HN and F antibodies appear to be neutralizing.[7] Initial studies of candidate vaccines focused on inactivated mixtures of PIV-1, PIV-2, and PIV-3 that, although capable of producing robust antibody responses, were not effective in protecting subjects against challenge.[130] A subsequent vaccine candidate used a modified Ankara vaccinia virus vector that expressed HN or F proteins of PIV-3. This vaccine protected nonhuman primates from lower respiratory tract disease but was ineffective in preventing upper respiratory infection and therefore was not pursued further.[131]

Currently, most efforts at PIV vaccine development have focused on reverse genetic technology applied to live-attenuated intranasally administered vaccines.[5] A live-attenuated bovine PIV-3 was evaluated but noted to have only modest seroconversion rates to human PIV-3.[5,132] A live-attenuated, cold-adapted PIV-3 virus derived from the JS strain (human PIV [HPIV]-3-cp45) has been studied and found to be safe and immunogenic in seropositive and seronegative infants and children. It appears to require two to three doses to result in durable immunity (84% of seronegative vaccine recipients developed a fourfold or greater increase in antibody titers).[5,133,134] A combined HPIV-3-cp45/RSV vaccine was found to result in antibody responses similar to those of the HPIV-alone vaccine.[135] More recently, another chimeric virus based on the HPIV-3-cp45 virus has been studied and found to be well tolerated and immunogenic in children 6 to 36 months of age. Existing data suggest that a three-dose regimen may be required in order to provide protective responses in infants younger than 6 months.[136] Likewise, two different recombinant bovine (rB)–human PIV-3 (rB/HPIV-3) live virus vaccine candidates have been studied. The rB/HPIV-3 was more restricted in replication in seronegative children than was rHPIV3-N(B), but it was demonstrated to induce significantly higher titers of hemagglutination inhibition antibodies against HPIV-3.[137] Another chimeric rB/HPIV-3 that also expresses RSV F or both F and G proteins has been developed and is undergoing clinical trials for prevention of both RSV and PIV.[5,138,139]

Although there are fewer candidates, there are also efforts to create PIV-1 and PIV-2 vaccines. These have focused on viruses produced through reverse genetics and another approach that uses a live-attenuated Sendai virus.[5,140–145] A live murine Sendai virus that shares antigenic similarities with HPIV-1 was administered intranasally to HPIV-1 seropositive children in a recent study, as a potential jennerian vaccine candidate. It was well tolerated, augmented antibody titers to HPIV-1, and is being considered for further testing in HPIV-1–seronegative children.[146]

Infection-control measures are crucial to prevent transmission of PIV in the health care setting. Localized outbreaks of PIV have been demonstrated in pediatric hospitals, wards housing immunocompromised patients, and nursing homes. Hospitalized patients with PIV infection should be placed on standard and contact precautions and should have a private room whenever possible.[147] Respiratory precautions are not necessary, because the droplets are large and do not aerosolize. A single-center study in HSCT patients found that requiring all individuals with direct patient contact to wear a surgical mask was associated with a reduction in respiratory viral infections, particularly PIV-3, during the most vulnerable period after HSCT.[72]

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157 Mumps Virus

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SHORT VIEW SUMMARY

Definition
- Mumps is an acute viral infection that most commonly manifests as nonsuppurative swelling and tenderness of the parotid or other salivary glands caused by the mumps virus.
- Less common manifestations of mumps include meningitis, encephalitis, epididymo-orchitis, oophoritis, and pancreatitis.

Epidemiology
- Mumps is endemic throughout the world, and humans are the only natural hosts for the virus.
- Incubation period is usually 16 to 18 days, with a range of 2 to 4 weeks.
- Before the introduction of the mumps vaccine in the United States in 1967, epidemics occurred every 2 to 5 years, with peak incidence between January and May.
- Since 1967 there has been greater than a 99% decline in the annual US incidence of mumps.
- Outbreaks of mumps have been reported throughout the world, including the United States, even in populations who have received the recommended two-dose measles-mumps-rubella (MMR) series.

Microbiology
- Mumps is an enveloped, single-stranded RNA virus.
- Only one serotype of mumps virus exists, but there are 13 genotypes.

Diagnosis
- The clinical diagnosis is made on the basis of a history of exposure and of parotid swelling and tenderness.
- The diagnosis is confirmed by isolation of mumps virus or detection of mumps nucleic acid by polymerase chain reaction from clinical specimens or the presence of mumps-specific immunoglobulin M (IgM) antibodies or a fourfold rise in mumps IgG antibodies in serum.

Therapy
- Therapy for mumps is symptomatic and supportive.

Prevention
- Immunization with live-attenuated mumps virus vaccine as part of the standard MMR vaccine at 12 months and 4 to 6 years of age is recommended for all children; a two-dose series of MMR is recommended for individuals beyond childhood who have not received the childhood series.
- The Advisory Committee on Immunization Practices recommended that a third dose of MMR be administered to individuals at increased risk of mumps during an outbreak (2018).

Mumps is an acute, generalized viral infection that occurs primarily in school-aged children and adolescents. The most prominent manifestation of this disease is nonsuppurative swelling and tenderness of the salivary glands, with one or both parotid glands involved in most cases. The disease is benign and self-limited, with one-third of affected persons having subclinical infection. Meningitis and epididymo-orchitis represent the two most important of the less frequent manifestations of this disease. As is characteristic of many viral infections, mumps is usually a more severe illness in persons past the age of puberty than in children and more commonly leads to extrasalivary gland involvement in these older patients. Although the use of effective vaccines has markedly reduced the incidence of mumps, the occurrence of outbreaks of mumps in the United Kingdom, Canada, United States, and elsewhere in recent years has raised concerns regarding the possible resurgence of the disease.

HISTORY

Hippocrates described mumps and its contagious characteristics in the fifth century BCE. In the late 1700s Hamilton emphasized the occurrence of orchitis as a manifestation of mumps. The experimental production of the disease in monkeys by Johnson and Goodpasture in 1934[1] provided the evidence that a filterable virus was present in the saliva of patients with mumps. In 1945 Habel reported the cultivation of mumps virus in the chick embryo.[2] Enders and colleagues[3] described the skin test and development of complement-fixing antibodies after mumps in humans. A killed-virus vaccine used in the early 1950s on human subjects achieved limited success,[4] and in 1966 Buynak and Hilleman[5] reported the development of an effective live-virus vaccine.

The etymology of the word *mumps* is unclear. It may arise from the English noun *mump,* meaning a lump, or from the English verb *to mump*, defined as "to be sulky"—a description of the characteristic facial expression. Alternatively, the term *mumps* has been ascribed to the mumbling speech pattern of the affected person. In the older literature mumps may have been called "epidemic parotitis."

VIROLOGY

Mumps virus is a member of the Paramyxoviridae family, which includes the following genera: *Rubulavirus* (mumps virus, New Castle disease virus, human parainfluenza virus types 2, 4a, and 4b); *Paramyxovirus* (human parainfluenza virus types 1 and 3); *Morbillivirus* (measles); and *Pneumovirus* (human respiratory syncytial virus). The complete mumps virion has an irregular spherical shape, with a diameter ranging from 90 to 300 nm and averaging about 200 nm. The nucleocapsid is enclosed by an envelope that has three layers and is about 10 nm thick.[6] The external surface is regularly studded with glycoproteins possessing hemagglutinin, neuraminidase, and cell fusion activity. The middle component of the envelope is a lipid bilayer acquired from the host cell as the virus buds off the cytoplasmic membrane. The innermost surface of the envelope is a nonglycosylated membrane protein that maintains the outer structure of the virus. The genome of the virus is contained in a nucleocapsid that is a helical structure composed of a continuous linear molecule of single-stranded RNA genome surrounded by symmetrically repeating protein subunits. The genome codes for eight proteins—the hemagglutinin-neuraminidase protein (HN), fusion protein (F), nucleocapsid protein (NP), phosphoprotein (P), matrix protein (M), hydrophobic protein (SH), and L proteins.[7] The P protein contains two nonstructural proteins, V and I. Antibodies to the F and HN proteins appear to be the most prominent determinants of immunity. Although only one serotype of mumps virus is known, there are 13 genotypes (A–M) that have been determined on the basis of

sequencing of the SH protein, which is the most variable protein among mumps strains.[8–10]

Mumps virus is ether sensitive by virtue of its lipid envelope. It is stable at 4°C for several days and at −65°C for months to years; however, repeated freezing and thawing may diminish viral activity.

The virus replicates in a variety of cell cultures and in embryonated hens' eggs.[11] For primary viral isolation, monkey kidney, human embryonic kidney, or HeLa cell cultures are used for primary isolation. Cytopathic effects, such as the appearance of intracytoplasmic eosinophilic inclusions, rounding of cells, or the fusion of cells into giant multinucleate syncytia, may be noted.[12] The presence of mumps virus is usually confirmed by the hemagglutination inhibition (HAI) test, which uses convalescent serum after mumps infection to inhibit the adsorption of chick erythrocytes added to mumps-infected epithelial cells.

EPIDEMIOLOGY

Mumps is endemic throughout the world. In the United States, before the licensing of live-attenuated mumps vaccine in 1967, epidemics occurred every 2 to 5 years.[13] Although the disease occurred throughout the year, the peak incidence was between January and May.[14] Epidemics have been reported in military populations and other closed communities, such as prisons, boarding schools, ships, and remote islands.[15,16] Meyer demonstrated that mumps is spread throughout the community by children in schools, with secondary spread to family members.[17] There has been more than a 99% decline in the annual US incidence of mumps since 1967, with an average of only 265 cases/year reported to the Centers for Disease Control and Prevention (CDC) from 2001–05; the seasonal variation that was evident in earlier years is no longer apparent.[18] However, there have been outbreaks of mumps reported from various sites, including the Netherlands,[8] United Kingdom,[19] United States,[20] and Canada.[21] In the 2006 outbreak in the United States, 6584 cases of mumps were detected; 85% of patients were in Iowa and the seven contiguous states; the highest attack rate was for the age group of 18 to 24 years, which comprised 29% of all cases, and 83% of this group attended college.[20] The outbreak virus was of genotype G, the same virus genotype that had caused an outbreak in the United Kingdom during 2004–06.[19] Surprisingly, for those patients with known vaccine status, only 13% had not received vaccine, and 63% had received two or more doses of mumps containing vaccine. The reasons for the outbreaks and the apparent vaccine failures are not clear and may have been multiple.[21,22] These include possible waning immunity and exposure pressure from crowded conditions in dormitories, where susceptible individuals may have gathered. Investigators demonstrated that in the Iowa outbreak, preoutbreak mumps antibody titers were lower among mumps case patients than in exposed but asymptomatic classmates.[23,24] Genotypic differences between the vaccine Jeryl Lynn strain (A) and the circulating mumps strain in outbreaks in the United States and United Kingdom (G) were present. Genotype G has been the predominant circulating mumps strain in the United States since 2006.[25] However, the genotype A virus vaccines were apparently effective in controlling genotype G outbreaks, so the role of genotype differences in vaccine failure, if any, is unclear. The epidemic rapidly subsided, so by 2008 there were only 376 cases of mumps reported to the CDC. From 2008–10, 3502 cases of mumps occurred in an orthodox Jewish community in New York City and nearby counties,[26] and in 2011 the California Department of Public Health reported 29 mumps cases on a college campus.[27] In the New York outbreak, most of the cases had previously received two doses of measles-mumps-rubella (MMR) vaccine; a third dose of MMR vaccine resulted in a rapid decline of the epidemic, suggesting that waning immunity could be bolstered even in populations with high two-dose coverage of MMR.[28] A study of 15 clusters of mumps in France in 2013 indicated that the "odds" of mumps increased for twice-vaccinated individuals by 10% for every year that had passed since the second dose.[29] On the basis of this and other studies, the French High Council of Public Health recommended that a third dose of MMR be given during outbreaks of mumps for individuals who had received their second dose more than 10 years before the outbreak.

A recent study of outbreaks of mumps in Ireland in 2008–09 showed that immunoglobulin G (IgG) levels to the circulating genotype G5 mumps strain needed to be greater than 40 relative units/mL to be correlated with anti-G5 neutralization activity in vitro.[30] Lower titers of serum neutralizing activity were seen in males compared with females with acute mumps infection. This is consistent with previous observations that males are more likely to be infected in such outbreaks.

In 2014 a large community outbreak of mumps occurred in central Ohio and involved local residents and students at Ohio State University. Four-hundred eighty-two cases were reported, with ages ranging from 6 months to 80 years.[31] There were 6369 cases of mumps reported to the CDC in 2016, which was the highest number of cases in a decade.[25] From January 1 to November 3, 2018, 2002 cases of mumps in the United States were reported to the CDC.[32]

Mumps is uncommon in infants younger than 1 year. Resistance to infection in this age group is based on passive immunity acquired by the placental transfer of maternal antibody. In the prevaccine era, greater than 50% of cases occurred in the 5- to 9-year-old age group, and 90% of the cases occurred in children younger than 14 years. In 2001 49% of infections were reported in persons older than 15 years. In the prevaccine era 80% to 90% of US adults older than 20 years were immune to mumps on the basis of natural infection. At present, in the United States immunity to mumps in children and most young adults relies on prior vaccination. Men and women have the same frequency of development of parotitis with mumps infection.[33]

Humans are the only known natural host; however, monkeys and other laboratory animals have been experimentally infected.[1] Although persistent infections in cultured cells are commonly established by mumps virus,[34] a carrier state is not known to exist in humans.

PATHOGENESIS

The virus is naturally transmitted via direct contact, droplet nuclei, or fomites and enters through the nose or mouth. More intimate contact is necessary to transmit mumps than for measles or varicella. The period of peak contagion is just before or at the onset of parotitis.

Experimental mumps infection has been produced in humans and monkeys by direct instillation of the virus into the Stensen duct.[1] However, the incubation period in this experimental model is shorter than in naturally occurring disease, and initial infection of the parotid gland does not explain the fact that meningitis or other manifestations of mumps infection may occur before the onset of parotitis. It has been suggested that, during the incubation period, the virus proliferates in the upper respiratory tract epithelium and viremia ensues, with secondary dissemination and localization to glandular and neural tissue.[35,36]

PATHOLOGY

Salivary glands from patients infected with mumps are rarely available for pathologic examination because of the benign course in the great majority of the cases. When parotid glands have been examined, diffuse interstitial edema has been found, along with a serofibrinous exudate consisting primarily of mononuclear leukocytes. Neutrophils and necrotic debris accumulate within the ductal lumen, and the ductal epithelium shows degenerative changes. The glandular cells are relatively spared but may also be involved with edema and overflow of the inflammatory reaction from the interstitial tissues. The multinucleate syncytia and intracytoplasmic eosinophilic inclusions that are occasionally seen in mumps-infected tissue culture are not present in vivo. When the pancreas or the testis is involved, the microscopic picture is similar to that seen in the salivary glands, except that interstitial hemorrhage and polymorphonuclear leukocytes are more frequently noted in orchitis. Local areas of infarction may occur because the vascular supply is compromised by increased pressure caused by edema within an inelastic tunica albuginea. When the process has been particularly severe, atrophy of the germinal epithelium may result, with accompanying hyalinization and fibrosis.

The description of brain involvement in mumps encephalitis has most often been that of postinfectious encephalitis characterized by perivenous demyelinization, perivascular mononuclear cuffing, and a generalized increase in microglial cells, with relative sparing of neurons.[37] However, descriptions of what appears to be primary mumps encephalitis that show widespread neuronolysis but no evidence of demyelinization have been reported.[38]

CLINICAL MANIFESTATIONS

The incubation period of mumps averages 16 to 18 days, with a range of 2 to 4 weeks. Characteristically, the prodromal symptoms are nonspecific and include low-grade fever, anorexia, malaise, and headache. Within 1 day the nature of the illness becomes apparent when the patient complains of an earache, and tenderness can be elicited by palpation of the ipsilateral parotid. The involved gland is soon visibly enlarged and progresses to a maximum size over the next 2 to 3 days. The most severe pain accompanies the period of rapid enlargement. At its height, parotitis results in lifting of the ear lobe upward and outward. Lesser degrees of enlargement can more readily be appreciated by viewing the patient from behind. The enlarged parotid gland obscures the angle of the mandible, whereas cervical adenopathy does not hide this anatomic landmark. Usually, one parotid gland enlarges 1 or 2 days after the other; however, mumps results in unilateral parotitis alone in one-quarter of patients with salivary gland involvement. The orifice of the Stensen duct is frequently edematous and erythematous. Trismus may result from the parotitis, and the patient may have difficulty with pronunciation and mastication. Ingestion of citrus fruits or juices typically exacerbates the pain. During the first 3 days of illness the patient's temperature may range from normal to 40°C. After parotid swelling has reached its peak, pain, fever, and tenderness rapidly resolve, and the parotid gland returns to normal size within 1 week. Complications of parotitis are rare but are reported to include sialectasia resulting in recurrent acute and chronic sialadenitis.[39]

Involvement of the other salivary glands may occur in conjunction with parotitis in up to 10% of cases but is rare as the sole manifestation of mumps infection (Table 157.1). Submandibular gland involvement mimics signs of anterior cervical lymphadenopathy. The sublingual glands are the least frequently inflamed during mumps infection; when involvement occurs, it is usually bilateral and may be associated with swelling of the tongue. Presternal pitting edema develops in 6% of patients with mumps, most commonly in those who have submandibular adenitis.[40] The proposed mechanism for the involvement of the tongue and presternal area is obstruction of the lymphatic drainage of those regions by enlarged salivary glands.

Pharyngolateral edema with dyspnea is a rare complication of mumps and may result in airway stenosis.[41] It is most often associated with submandibular gland swelling and is thought to be caused by local inflammation and circulatory disturbance of lymphatic flow. Cases generally respond to administration of steroids, but some cases have required tracheotomy.[41]

Central nervous system (CNS) involvement is the most common extrasalivary gland manifestation of mumps. As documentation of the remarkable neurotropism of this virus, Bang and Bang[42] reported the presence of cerebrospinal fluid (CSF) pleocytosis in 51% of 255 patients with mumps but without other evidence of meningitis. Clinical meningitis occurs in 1% to 10% of persons with mumps parotitis,[43] but, on the other hand, only 40% to 50% of patients with mumps meningitis, confirmed by serology or viral isolation, have parotitis.[43–46] Meningeal symptoms, like any of the other manifestations of mumps infection, may occur before, during, after, or in the absence of parotitis. Its onset averages 4 days after the appearance of salivary gland involvement but may be as early as 1 week before or as late as 2 weeks after parotitis.[42–45] Men are afflicted three times as often as women,[43–46] but the age distribution is the same as for uncomplicated mumps. Ritter has noted that mumps meningitis with parotitis is most frequent in the spring, whereas meningitis without parotitis is most frequent in summer.[44] The typical clinical features associated with viral meningitis are present—that is, headache, vomiting, fever, and nuchal rigidity. Lumbar puncture yields CSF containing 10 to 2000 white blood cells (WBC)/mm^3. The predominating cells are usually lymphocytes, but 20% to 25% of patients have a polymorphonuclear leukocyte predominance.[45] Protein levels are normal to mildly elevated, and 90% to 95% of patients have a CSF protein content less than 70 mg/dL.[45,46] Hypoglycorrhachia (CSF glucose concentration <40 mg/dL) is reported in 6% to 30% of the patients[45–47] and appears to be more common than in other viral meningitides. These CSF abnormalities may persist for 5 weeks or longer.[44,47] The finding of a depressed CSF glucose level with a moderate-to-marked pleocytosis may cause the physician to consider bacterial meningitis in the differential diagnosis, especially if neutrophils predominate, as they may early in the disease. As in other cases of meningitis, when mononuclear cells prevail in the CSF, tuberculous and fungal disorders should be considered.

Abatement of fever by lysis and resolution of symptoms generally occur 3 to 10 days after the onset of illness. The meningitis is benign, with complete recovery and an absence of sequelae. Before the introduction of the live-attenuated mumps vaccine in 1967, mumps accounted for approximately 10% of cases of aseptic meningitis in the United States. At present aseptic meningitis is rarely attributed to mumps.

Encephalitis is reported to occur in from 1 in 6000[48] to 1 in 400[49] cases of mumps. The former ratio probably represents a more accurate estimate. There appears to be a bimodal distribution of cases according to the time of onset—an early group in which onset coincides with the presence of parotitis and a larger late group in which the condition develops 7 to 10 days after the onset of parotitis. As noted earlier in the section "Pathology," early-onset encephalitis represents direct damage to neurons as a result of viral invasion, whereas late-onset disease is a postinfectious demyelinating process related to the host response to infection. These two processes probably represent the ends of a continuum of disease. Some patients die after the primary viral invasion of the brain, and some of those who survive produce antibodies to the virus or neural breakdown products and develop an "autoimmune" reaction. The clinical features are generally those of nonfocal encephalitis; in addition to marked changes in the level of consciousness, neurologic findings may include convulsions, paresis, aphasia, and involuntary movements. CSF values are similar to those in uncomplicated meningitis. Fever is high and, characteristically, temperatures of 40° to 41°C are present. Neurologic manifestations and fever gradually resolve over a period of 1 to 2 weeks. Sequelae such as psychomotor retardation and convulsive disorders are reported,[44–46] but their frequency cannot be determined from the available data. Death occurs in 1.4% of reported cases.[49]

Through the mid-1960s, mumps was the leading recognized cause of viral encephalitis in the United States, being responsible for 20% to 30% of cases. However, by 1981 it represented only 0.5% of cases of viral encephalitis nationwide, and by the 1990s mumps encephalitis was rare. The major factor accounting for this change was an effective mumps immunization program.

The term *meningoencephalitis* is frequently used when describing patients with various degrees of CNS involvement.[38,43,44,47,50] This term should be eliminated in reference to mumps because it confuses a common and essentially benign condition (meningitis) with a relatively uncommon and serious illness (encephalitis) that might result in

TABLE 157.1 Frequency of Common Clinical Manifestations of Mumps

MANIFESTATION	FREQUENCY (%)
Glandular	
Parotitis	60–70
Submandibular and/or sublingual sialadenitis	10
Epididymo-orchitis[a]	25 (postpubertal men)
Oophoritis[a]	5 (postpubertal women)
Neural	
Cerebrospinal fluid pleocytosis	50
Meningitis	1–10
Encephalitis	0.1
Transient high-frequency deafness	4
Other	
Electrocardiographic abnormalities	5–15
Renal function abnormalities (mild)	>60

[a]Rare before puberty and usually unilateral.

neurologic residua or death. Clearly, many patients with mumps meningitis may have lethargy, as may a large percentage of those with any viral infection, such as influenza. However, the presence of profound changes in the level of consciousness or other findings suggestive of supratentorial involvement indicates the clear diagnosis of encephalitis as distinct from the ambiguous designation of meningoencephalitis. Although nuchal rigidity and CSF pleocytosis may be present in patients with encephalitis, the meningeal component is a trivial aspect of this illness.

Transient high-frequency-range deafness has been reported in 4.4% of cases of mumps in a military population.[51] Permanent unilateral deafness occurs in 1 in 20,000 cases of mumps.[52] The onset of otologic symptoms may be gradual or abrupt; vertigo is frequently present. On subsequent testing vestibular function has been normal.

Other neurologic syndromes rarely associated with mumps include cerebellar ataxia,[53] facial palsy,[54] transverse myelitis,[55] ascending polyradiculitis (Guillain-Barré syndrome),[56] and a poliomyelitis-like syndrome.[57] There are now several well-documented cases of aqueductal stenosis and hydrocephalus developing after CNS infection caused by mumps.[58–60] Experimental and clinical reports have clearly implicated mumps as the probable causative agent of this disorder.[61–63]

Epididymo-orchitis is the most common extrasalivary gland manifestation in the adult. It develops in 20% to 30% of postpubertal male adolescents with mumps infection and is bilateral in one of six of those with testicular involvement.[64,65] Although it has been reported in infancy, it is rare before puberty. Two-thirds of cases occur during the first week of parotitis and another 25% arise during the second week.[64] However, gonadal involvement may precede parotitis or occur as the only manifestation of mumps. The onset is abrupt, with temperatures in the range of 39° to 41°C, chills, headache, vomiting, and testicular pain. Genital examination reveals warmth, swelling, and tenderness of the involved testicle and erythema of the scrotum. Epididymitis is present in 85% of cases and usually precedes the orchitis, but it is rare without orchitis. The testis may be enlarged to three to four times its normal size. Constitutional complaints and fever generally parallel the severity of gonadal involvement. Fever resolves in 84% of patients within 5 days. Pain and swelling resolve shortly after defervescence. However, tenderness may persist for longer than 2 weeks in 20% of the cases.[64] Early in convalescence a loss of turgor may be appreciated. When testes are examined months to years later, some degree of atrophy is noted in 50% of patients.

The anxiety engendered by mumps orchitis is difficult to allay. The psychological fears of sexual impotence and sterility far outweigh the potential debility from testicular atrophy. Clearly, most men who have unilateral orchitis need fear nothing other than a possible cosmetic imbalance. Even those with bilateral involvement should be assured that impotence (other than psychogenic) is not a sequela and that sterility is rare. In large surveys of infertile men, mumps is infrequently implicated as the causative disorder. Twenty-eight cases of testicular malignancy in men with atrophy of the testis due to mumps orchitis have been reported.[66]

Oophoritis develops in 5% of postpubertal women with mumps. Symptoms include fever, nausea, vomiting, and lower abdominal pain. Impaired fertility and premature menopause have been reported as a consequence of ovarian involvement but must be considered to be rare.[67]

Joint involvement during mumps is noted infrequently in adults and rarely in children.[68,69] Migratory polyarthritis is the most frequently described clinical form. Monarticular arthritis and arthralgia have also been reported; both large and small joints are involved. Symptoms most commonly start 10 to 14 days after the onset of parotitis and may last up to 5 weeks. The process resolves spontaneously without residual joint damage.

Pancreatitis is manifested by severe epigastric pain and tenderness accompanied by fever, nausea, and vomiting. It is uncommon as a severe illness; however, many affected persons may complain of mild degrees of upper abdominal discomfort.

Electrocardiographic changes appear in up to 15% of patients with mumps; the most common abnormalities are depressed ST segments, flattened or inverted T waves, and prolonged P-R intervals.[70,71] Clinically manifested myocarditis is rare; however, deaths associated with myocarditis have been reported during the acute illness and after a chronically progressive deteriorating course.[70,71]

Utz and colleagues[72] have prospectively evaluated renal function in 20 young adult Navy servicemen admitted with mumps. These investigators discovered transient mild-to-moderate abnormalities of urinary concentration, creatinine clearance, and phenolsulfonphthalein excretion in most of this group. Hughes and colleagues[73] have reported two deaths related to mumps-associated nephritis.

A variety of other manifestations have accompanied mumps infection but must be considered extremely rare; these include thyroiditis,[74] mastitis,[75] prostatitis,[76] hepatitis,[77] and thrombocytopenia.[78]

COMPLICATIONS

Gestational viral infections were extensively investigated in a controlled cohort study by Siegel and colleagues.[79–81] They observed excess fetal deaths when mumps developed during the first trimester; second- and third-trimester mumps infections were not associated with increased fetal mortality.[79] Low birth weight (<2500 g) was identified in 7.7% of infants born to mumps-infected mothers, compared with 3.3% of a control group; this is not, however, a statistically significant difference. Although the number of cases was small, when the data were analyzed with respect to the onset of infection, the effect on birth weight was greatest when mumps occurred in the first trimester.[80] A variety of congenital malformations have been described in pregnancies complicated by maternal mumps[82]; however, these anomalies are described in single case reports without comparison with an uninfected control population. As reported by Siegel and colleagues,[81] occurrence rates of major congenital defects were equal in both mumps and control newborn populations; even when the data were analyzed by trimester, no trends could be established. Similar results were obtained by a British team after reviewing 500 pregnancies complicated by maternal mumps.[83]

St. Geme and colleagues[84] have suggested an "embryopathic" relationship between intrauterine mumps infection and endocardial fibroelastosis (EFE) on the basis of the presence of skin test reactivity to mumps antigen in a high percentage of the EFE patients. Experimentally induced infection of the chick embryo has added histopathologic support to this association.[85] Although some observers have disputed that mumps plays a causative role,[86] studies using polymerase chain reaction (PCR) techniques have demonstrated mumps viral RNA in greater than 70% of samples of myocardium from patients with autopsy-proven EFE.[87] There has been a marked decline in the incidence of EFE in the past 3 decades, corresponding to the declining incidence of mumps.

A similar controversy exists over the possible role of mumps in the etiology of juvenile diabetes mellitus. Diabetes, transient or permanent, which developed soon after mumps, has been the subject of a number of case reports.[88,89] However, it is not clear whether this is simply coincidental. Epidemiologic studies have demonstrated a 7-year periodicity in the incidence of both mumps and childhood diabetes, with a 3- to 4-year lag time between their respective peaks.[90] Coxsackievirus B4 has also been epidemiologically linked to diabetes.[91] Although the frequency of EFE has declined in recent years, there has not been a decline in the frequency of juvenile diabetes mellitus coincident with the decreasing frequency of mumps after introduction of the mumps vaccine.

IMMUNOLOGY

After clinical or subclinical mumps infection, a variety of immunologic responses can be demonstrated. Complement-fixing antibodies directed against the NP protein (historically, S antigen) appear rapidly; sometimes they are present at the onset of clinically apparent illness. Antibody titers against the HN protein (historically, V antigen) rise more slowly and peak at about 2 to 4 weeks after the beginning of disease.[92] However, anti-NP antibody titers decline rapidly over a period of several months to undetectable levels, whereas anti-HN antibody titers drop more slowly and persist for years. This pattern of response provides the possibility of a serologic diagnosis of mumps from a single serum specimen. An acute-phase serum demonstrating a high anti-NP and low anti-HN titer or a high anti-NP and high anti-HN titer can be interpreted as evidence of current or recent infection, respectively. The presence in

serum of only anti-HN antibodies would indicate a more remote infection with mumps. IgM antibodies to mumps are the earliest humoral responses and usually fall within 2 to 6 months. IgM anti-NP antibodies detected by capture or enzyme-linked immunosorbent assay (ELISA) are the most sensitive early serologic responses and are used by the CDC to detect acute or recent infection (see later).

Neutralizing antibodies appear during convalescence. They are directed against HN and F proteins, and detectable titers persist for years. Although assays for these antibodies constitute the most reliable test to determine whether a person is immune to mumps, such assays are cumbersome and not routinely performed. Assays for HAI antibodies, which also develop after the onset of mumps, are the simplest of the serologic studies, but results are unreliable because of potential cross-reaction with other paramyxoviruses. ELISAs for antibody to mumps have been developed[93,94] and are widely available.

Delayed hypersensitivity to an intradermally administered mumps skin test antigen develops between 3 weeks and 3 months after mumps.[3] The skin test was widely used as a measure of immunity to mumps and as a test for the competence of delayed hypersensitivity. The use of mumps skin test antigen to determine immunity to mumps has been abandoned because of the variability of lots of the skin test antigen and of the occurrence of false-positive and false-negative results.

Transplacental transfer of maternal mumps complement-fixing, HAI, and neutralizing antibodies has been demonstrated.[95] Titers in maternal and cord serum are almost identical. Neutralizing antibodies persist for several months and account for the rarity of mumps in young infants and for the lack of response to immunization in this age group. One attack of mumps, whether inapparent or clinically manifested, confers lifelong immunity.

DIAGNOSIS

Historically, the diagnosis of mumps has been made on the basis of a history of exposure and of parotid swelling and tenderness accompanied by mild-to-moderate constitutional symptoms.

The WBC and differential counts in mumps are normal, or there may be a mild leukopenia with a relative lymphocytosis. When meningitis, orchitis, or pancreatitis is present, leukocytosis with a shift to the left is most commonly encountered. The serum amylase level is elevated in the presence of parotitis and may remain abnormal for 2 to 3 weeks. Serum amylase levels may also be elevated in the absence of clinical salivary gland involvement. Mumps pancreatitis also increases amylase levels; differentiation from salivary gland amylase may be achieved by isoenzyme analysis or serum pancreatic lipase determinations.

The typical CSF findings in mumps meningitis have been described previously. Similar, although less marked, CSF abnormalities are present in half of patients with mumps parotitis but without apparent CNS involvement. In a patient with aseptic meningitis an elevated serum amylase level should suggest mumps infection.

Laboratory confirmation of typical mumps is unnecessary. However, when parotitis is absent or recurrent, when extrasalivary gland manifestations are prominent, or when documentation of the presence of a specific viral disorder is desired, a variety of diagnostic aids can be used.

The definitive diagnosis of mumps depends on serologic studies, viral isolation, or PCR assay. The presence of IgM antibodies, as determined by ELISA or a fourfold rise between acute and convalescent sera on complement fixation, HAI, ELISA, or neutralization testing, confirms the diagnosis. The HAI test can be affected by heterologous antibody responses to parainfluenza virus infection. Because parotitis can be caused by parainfluenza type 3 virus,[96] serologic testing and virus isolation studies for parainfluenza type 3 virus should be undertaken if the HAI test is used in the diagnosis of mumps. Immunity to mumps is usually assessed by ELISA. This assay combines ease of performance with reliability. Reverse transcriptase PCR assays that are highly sensitive and specific have been developed and appear to be significantly more sensitive than tissue culture isolation methods.[7,97,98]

Virus is usually present in saliva for about 1 week, from 2 to 3 days before to 4 to 5 days after the onset of parotitis.[99] However, virus has been isolated from saliva as early as 6 days before and as late as 9 days after the first signs of salivary gland involvement. In addition, virus may be recovered from the saliva of persons with inapparent infection or those who manifest only extrasalivary gland signs.[100] A recent review of viral shedding data by the CDC, American Academy of Pediatrics, and Healthcare Infection Control Practices Advisory Committee has concluded that virus shedding is relatively low by 5 days after onset of parotitis and recommended that isolation of patients is not necessary for more than 5 days after clinical illness in the hospital or community setting.[101] The virus is frequently isolated from the CSF in patients with clinical meningitis during the first 3 days of meningeal symptoms[43] and is present as late as the sixth day of CNS disease. Viruria has been detected during the first 2 weeks of illness; in one study 72% of urine specimens during the first 5 days of illness yielded a positive culture.[72] Viremia has rarely been detected and has been found only during the first 2 days of illness.[35,36] Mumps viral RNA has been detected by PCR assay in clinical specimens from patients with mumps infection and in throat swabs of healthy children after administration of mumps vaccine.[102–104]

DIFFERENTIAL DIAGNOSIS

A variety of entities may simulate mumps but can be easily differentiated from mumps on the basis of chronicity or associated symptoms. Infectious processes involving parotid glands are most likely to be confused with mumps because of their acute onset and associated fever. Parainfluenza 3 virus, coxsackieviruses, and influenza A viruses have been reported to cause acute parotitis.[96,105,106] These entities can be differentiated from mumps only by viral culture or serology. In a study of 101 cases of sporadic nonoutbreak cases of parotitis in the United States from 2009–11, no specimen was positive for mumps virus; 38 specimens were positive for other viruses, including Epstein-Barr virus, human herpesvirus 6, and parainfluenza; and 17% of cases tested were positive for mumps IgM antibody.[107] Bilateral parotid swelling is often seen in children with human immunodeficiency virus (HIV) infection. Suppurative parotitis, most often caused by *Staphylococcus aureus* or gram-negative organisms, usually occurs in the postoperative period, in premature newborns, or in debilitated patients with poor oral intake. The gland is warm, hard, and extremely tender; the overlying skin is erythematous. Massage of the parotid expresses purulent drainage from the Stensen duct.

Parotid enlargement caused by drugs or metabolic disorders is usually bilateral and asymptomatic. Phenylbutazone, thiouracil, iodides, and phenothiazines have been implicated in this condition.[76] Diabetes mellitus, malnutrition, cirrhosis, and uremia are among the metabolic disorders that can cause parotid swelling.[76]

Tumors, cysts, and obstruction caused by stones or stricture are usually unilateral. Rare conditions that may mimic mumps include Mikulicz syndrome, Parinaud syndrome, uveoparotid fever of sarcoidosis, and Sjögren syndrome.

THERAPY

Therapy for mumps parotitis is symptomatic and supportive. Treatment with analgesic-antipyretics, such as aspirin, acetaminophen, or nonsteroidal antiinflammatory drugs, relieves pain caused by salivary gland inflammation and reduces fever. Topical application of warm or cold packs to the parotid may also relieve discomfort. Intravenous fluid administration may be necessary for patients with meningitis or pancreatitis who have persistent vomiting.

Management of orchitis is purely symptomatic. Bed rest, narcotic analgesics, support of the inflamed testis with a "bridge," and ice packs make the patient feel more comfortable. An anesthetic block of the spermatic cord with 1% procaine hydrochloride may alleviate severe pain.[108] There is no convincing evidence that the use of steroids or diethylstilbestrol or incision of the tunica albuginea produces more rapid resolution of the orchitis or prevents subsequent atrophy. Interferon-α2b administered to four men with bilateral mumps orchitis resulted in prompt resolution of symptoms, with no evidence of testicular atrophy or oligospermia during follow-up study.[109] Further investigation to establish the efficacy of this treatment has not been carried out.

Gellis and colleagues[110] have shown that 20 mL of mumps immune globulin administered intramuscularly to adult men with mumps reduces the incidence of orchitis from 27.4% to 7.8%. However, mumps immune globulin is no longer commercially available.

PREVENTION

As noted, recommendations for the management of patients with mumps include isolation for 5 days after the onset of parotid swelling to prevent the spread of infection to susceptible persons.[101] This measure may be of little value, particularly in closed populations, such as schools or hospitals,[111] because virus is present in saliva days before parotitis develops and because those with clinically inapparent infection can shed virus.

Passive protection to exposed susceptible persons may have been afforded by mumps immune globulin, available in the past. However, Reed and colleagues[16] reported that use of mumps immune globulin during an epidemic in Alaska did not reduce clinical parotitis or inapparent infection rates and did not diminish the incidence of meningitis and orchitis.

Active immunization with the Jeryl Lynn strain of attenuated mumps virus vaccine has been available in the United States since December 1967. The vaccine is prepared in chick embryo cell culture.[5] A single subcutaneous immunization produces protective levels of mumps-neutralizing antibodies in greater than 95% of vaccinees.[5] Although the antibody levels produced are lower than after natural infection, adequate titers are maintained for at least 10.5 years.[112] Adverse reactions to the vaccine are uncommon; transient suppression of tuberculin-delayed hypersensitivity has been reported, and parotitis and orchitis have been recognized rarely. Vaccine virus is not present in secretions of immunized children. In Japan aseptic meningitis associated with mumps vaccine virus occurred in 0.05% to 0.3% of recipients of the Urabe AM 9 mumps vaccine; manifestations began 2 to 4 weeks after immunization.[113,114] US studies did not reveal evidence of an increased risk of aseptic meningitis after administration of the Jeryl Lynn strain of mumps vaccine.[115]

All children older than 12 months should be immunized. Vaccination should take place at 12 to 15 months and again at 4 to 6 years of age, as part of immunization with the combined live measles-mumps-rubella (MMR) virus vaccine. Most states now require evidence of immunity to mumps (i.e., documented immunization, physician-diagnosed disease, or antibody studies) for school entrance and attendance (see Chapter 316). A two-dose immunization regimen is recommended for all adolescents and health care personnel without evidence of mumps immunity. Other adults should receive at least one dose of vaccine. Immunization after exposure may not provide protection from natural infection.

Based on the results of a study on the effectiveness of a third dose of MMR vaccine to control a mumps epidemic at the University of Iowa in 2015–16, where 98.1% of students had previously received two doses of MMR,[116] the Advisory Committee on Immunization Practices recommended in 2018 that a third dose of MMR vaccine be administered to persons at increased risk of mumps during an outbreak.[25]

As with other live-virus vaccines, mumps vaccine should not be administered to pregnant women, patients receiving immunosuppressive therapy, or those with severe febrile illnesses, advanced malignancies, or congenital or acquired immunodeficiencies. Serious reactions to the mumps component of MMR have not been reported in limited studies in HIV-infected patients. However, a fatal case of measles pneumonitis occurred in a 21-year-old man with advanced HIV disease who was vaccinated with MMR vaccine; therefore it should not be administered to such patients (see Chapter 316).[117] Individuals with HIV infection who are not severely immunocompromised may be immunized with MMR vaccine.

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The complete reference list is available online at Expert Consult.

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158 Respiratory Syncytial Virus

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SHORT VIEW SUMMARY

Definition
- Respiratory syncytial virus (RSV) causes acute upper and lower tract respiratory illnesses.

Epidemiology
- RSV circulates annually during the winter months in temperate climates.
- RSV is the leading cause of bronchiolitis in infants.
- Reinfection is common throughout life and causes severe disease in elderly adults and immunocompromised individuals.
- RSV is primarily transmitted by direct contact with infected individuals or their secretions.

Microbiology
- RSV is an enveloped nonsegmented RNA virus in the *Pneumoviridae* family.
- RSV isolates can be classified into antigenically distinct groups, A and B.

Diagnosis
- Clinical diagnosis in infants is relatively accurate during the winter months; however, in older children and adults, laboratory confirmation by culture, antigen detection, or reverse-transcriptase polymerase chain reaction is necessary.

Therapy
- Treatment for most infants and adults is mainly supportive only.
- Aerosolized ribavirin, a nucleoside analogue, can be considered for administration to high-risk, highly immunocompromised patients; other therapies are under investigation.

Prevention
- Attention to infection control measures such as hand hygiene and contact precautions can reduce the spread of RSV.
- Palivizumab, a humanized neutralizing monoclonal antibody to RSV, is beneficial for certain high-risk infants including infants with underlying cardiac and pulmonary disease and low gestational age.
- New vaccines and monoclonal antibodies for the prevention of RSV are under active development.

Respiratory syncytial virus (RSV) is the major cause of lower respiratory tract illness in young children.[1–8] All people will have experienced RSV infection within the first few years of life. However, immunity is not complete, and reinfection is common. Although serious infections most commonly occur during the first few years of life, RSV infections contribute substantially to the morbidity caused by acute upper and lower respiratory tract infections among older children and adults. Estimated national hospitalization charges for bronchiolitis in children less than 2 years of age exceeded $1.7 billion in 2009.[1] The mortality related to RSV in developing countries and the morbidity and costs associated with RSV infections in older adults are being increasingly recognized.[9–12]

HISTORY

RSV was first discovered in 1956 when Morris and coworkers[13] isolated a new virus from chimpanzees with colds and coryza, and was originally named *chimpanzee coryza agent* (CCA). Subsequently, Chanock and colleagues[14] confirmed that the agent caused human illness when they obtained isolates indistinguishable from CCA from two children with respiratory illness. When specific neutralizing antibody to CCA was found in most school-aged children, CCA was more appropriately renamed RSV to denote its clinical and laboratory manifestations.

VIROLOGY

Classification

Human RSV belongs to the order Mononegavirales, family Pneumoviridae.[15] The two genera within the Pneumoviridae are *Metapneumovirus,* containing human metapneumovirus and *Orthopneumovirus,* which contains human RSV and the morphologically and biologically similar bovine, ovine, and caprine RSV.

Viral Structure and Characteristics

RSV is an enveloped, medium-sized (120–300 nm) RNA virus with a nonsegmented, single-stranded, negative-sense genome (Figs. 158.1 and 158.2).[16,17] The viral envelope has transmembrane surface glycoprotein spikes 12 nm in length, and on electron microscopy the virus can be identified as early tubular structures and later more mature spherical structures. (Fig. 158.3).[16,17]

The viral RNA consists of approximately 15,222 nucleotides containing 10 genes (see Fig. 158.2).[16,18] Each gene encodes a single protein except for the *M2* gene, which possesses two overlapping open reading frames encoding two separate proteins (M2-1 and M2-2, the transcription processivity factor and a transcriptional regulatory protein, respectively). Four proteins, N (nucleoprotein), P (phosphoprotein), L (polymerase), and M2-1, are associated with the RNA-containing nucleocapsid complex. The envelope has three transmembrane surface proteins, F (fusion), G (attachment), and SH (proposed viroporin protein), that are important for viral infectivity.[16,19] In addition, a truncated secreted form of G (Gs) is transcribed from a second start codon. The M (matrix) protein accumulates at the inner surface of the envelope and is important in viral morphogenesis.[17] Two proteins, NS1 and NS2, are nonstructural proteins that inhibit cellular type I and III interferon activity and subsequently affect the adaptive immune response to RSV.[16,20]

The two glycosylated surface proteins, F and G, are major immunoprotective antigens and targets for antibody-mediated neutralization.[21] The G protein is the primary mediator of attachment of the virus by binding to the CX3C receptor on respiratory epithelial cells and immune cells, although the F protein also can facilitate viral attachment by binding to cell surface nucleolin.[22–24] After attachment in the prefusion form, F undergoes structural changes into a postfusion form that initiates viral penetration by fusing viral and host cell membranes.[21] The prefusion F displays a greater number of neutralizing epitopes than the postfusion F, some of which are highly potent.[21]

Laboratory Properties

RSV poorly withstands slow freezing, thawing, or changes in pH. At 55°C, infectivity rapidly diminishes; at room temperature, only 10% infectivity remains at 48 hours; at 4°C, only 1% remains after 7 days.[25] RSV is inactivated quickly at pH <5 or contact with ether, chloroform, and detergents. At room temperature, RSV in secretions of patients

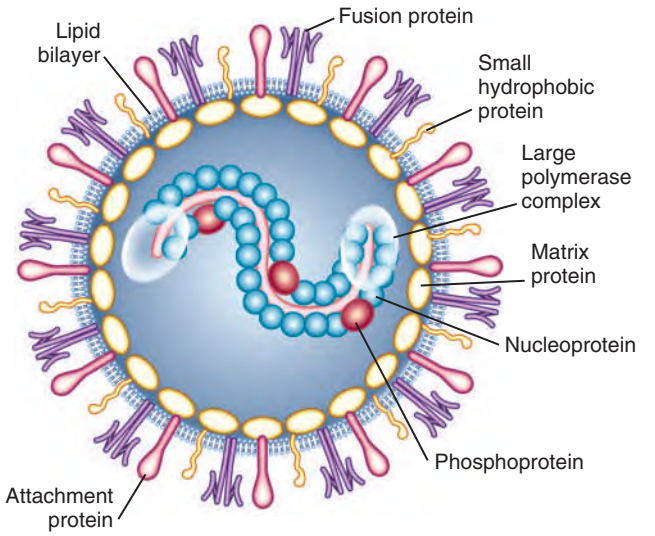

FIG. 158.1 Structure of respiratory syncytial virus. *(Modified from Hall CB. Respiratory syncytial virus and parainfluenza virus.* N Engl J Med. *2001;344:1917–1928.)*

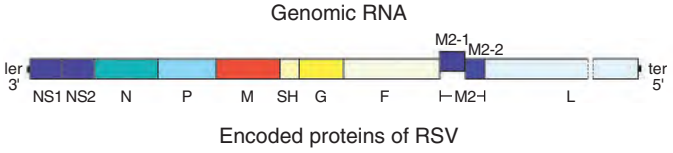

FIG. 158.2 Simplified representation of the negative-sense RNA genome of respiratory syncytial virus *(RSV)* and the encoded proteins. The genome is shown 3′ with the leader extragenic region *(ler)* and with the 5′ trailer extragenic region *(ter)*. The viral genes are depicted by the divided bars. Each viral gene transcribes a single messenger RNA encoding a single protein with the exception of M2 messenger RNA, which transcribes two proteins, M2-1 and M2-2.

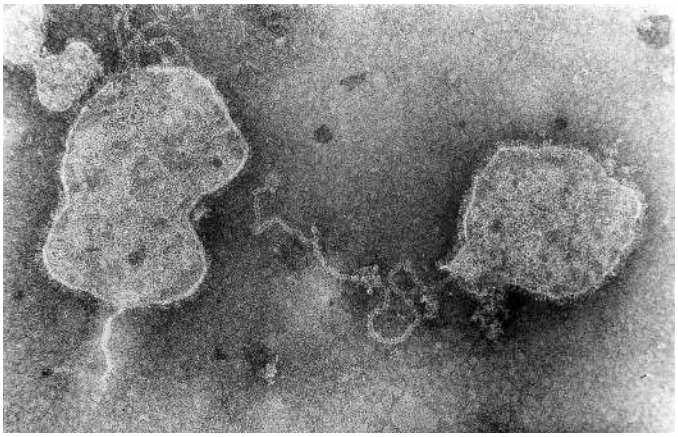

FIG. 158.3 Negative contrast electron micrograph of respiratory syncytial virus.

may survive on nonporous surfaces such as countertops for 3 to 30 hours and on porous surfaces such as cloth and paper tissue usually for less than 1 hour.[26] The infectivity of RSV on the hands is variable but is usually less than 1 hour.

Human heteroploid cell lines (HEp-2, HeLa, and A549) are usually preferred for primary isolation, but RSV may also be recovered in human kidney, amnion, and diploid fibroblastic cells and monkey kidney cells. Characteristic cytopathic effect may be first detected after an average of 3 to 5 days, and typical syncytia develop approximately 10 to 24 hours later. RSV can also infect macrophages, dendritic cells, and T and B cells.

Infection in Animals

Humans and chimpanzees are the only natural hosts for human RSV, although a variety of small animal species may be experimentally infected.[27] Although many animal models develop upper respiratory tract infection, their lack of symptomatic lower respiratory tract limits their utility. Rodents are the most commonly used models, particularly cotton rats and mice, but replication of RSV is only semipermissive. The ferret model has been used recently, as it demonstrates several characteristics of human illness and transmission.[28]

EPIDEMIOLOGY

Distribution and Seasonal Occurrence

In every geographic area studied, RSV infections are ubiquitous and clinically similar. However, the seasonality varies according to geography and climate.[29,30] RSV is singular in its ability to produce a major burden of disease every year.[1,6] In temperate climates, outbreaks occur primarily in late fall through early spring and spread across the United States over 20 or more weeks, generally from October to May. In warmer climates, RSV activity may be more prolonged or even present throughout the year.[29–32] In wet tropical climates, RSV peaks during rainy periods, whereas it peaks during cooler periods in drier climates.[33] Factors that initiate and terminate the recurring patterns of RSV activity remain elusive.[32,34,35] A complex interaction of local meteorologic conditions may explain part of the geographically variable epidemiologic patterns.[36] Because the only source of RSV infection is an infected individual, human behavior is an indefinable factor integral to its transmission.[37]

Antigenic Variation

Strain differences among RSV isolates may also affect the intensity, severity, and diversity of RSV outbreaks.[38–47] RSV isolates are divided into two major antigenic groups, A and B, each with multiple genotypes—up to 11 for group A and 23 for group B viruses.[41] The two major groups have 81% nucleotide identity, but some proteins between A and B strains vary appreciably, with the most diversity in the G protein, followed by M2-2 and SH proteins. This is reflected in antigenic relatedness between the two groups of only 1% to 7% for G proteins compared with 50% for F proteins.

Strains of both groups circulate simultaneously, but the proportions of A and B vary, as do genotypes.[39,40,42,43] Analyses of strains collected over decades and from diverse areas suggest that pressure of the population's immunity may result in a selective advantage for dominance of strains most divergent from those that have recently circulated. Recently emerged RSV viruses, containing unique 20–amino-acid and 26–amino-acid duplications in the group B and A G proteins, respectively, have spread throughout the world, suggesting transmission advantage over prior strains.[44,45] The relationship of circulating genotypes to illness severity and manifestations in young children has been inconsistent and thus inconclusive.[41] Several reports indicate that group A ON1 strains, originally isolated in Ontario, Canada, are less severe than strains lacking the 24-amino acid duplication.[41] The relationship between the substantial antigenic diversity of the G protein to reinfection with RSV has not been established.

Epidemiology Manifestations

RSV outbreaks may vary year to year in size and intensity.[1–3,48,49] Severe lower respiratory tract illness from RSV in previously healthy children occurs most frequently in the first year of life and is almost always associated with primary infection.[50,51] Essentially all children experience RSV infection within the first several years of life.[52–54]

Prevalence and Incidence

RSV is the most frequent cause of bronchiolitis and is estimated to cause 40% to 90% of bronchiolitis hospitalizations and up to 50% of pneumonia admissions among infants.[5,49–51,55] The remaining cases are caused by rhinovirus, parainfluenza viruses, human metapneumovirus, and influenza virus.[56] Of tracheobronchitis cases, 10% to 30% have been associated with RSV infection, but only 2% to 10% of croup cases have been associated with RSV infection. Bronchiolitis is the leading cause of all hospitalizations among infants in the United States. Overall, 172,000 children younger than 5 years of age are reported to be hospitalized

annually with RSV infection in the United States.[4,6,7] The yearly rates of RSV hospitalizations estimated from national databases have been variable, ranging from 2 to 44 per 1000 children within the first 2 to 5 years of life.[48,50,51,57,58] Children within the first year of life consistently had the highest rates of hospitalization for bronchiolitis and other RSV-associated illnesses, and the preponderance of admissions were in infants younger than 6 months.[7,51] Population-based studies in the United States indicated current hospitalization rates of 17 per 1000 children younger than 6 months and 3 per 1000 children younger than 5 years.[3,49,51] The highest hospitalization rates (25.9/1000) were in infants 1 month of age, slowly decreasing thereafter.[51] These rates are similar to rates derived from RSV-coded hospitalization data and are more than three times the rates from parainfluenza or influenza viral infections over 4 years of surveillance among the same population.[59,60] RSV hospitalization rates from European countries have been generally similar, ranging from 2.5 to 11 per 1000 children within the first 4 years of life and highest among infants younger than 12 months of age at 19 to 22 per 1000 children.[8,50,61–63]

Lower respiratory tract infections from RSV in developing countries are estimated to be twice as prevalent as in developed countries.[8] Worldwide, RSV is estimated to cause 33.1 million RSV acute lower respiratory infections annually and 3.2 million hospitalizations in children younger than 5 years, most of which are in developing and low-income countries.[8] Despite its frequency, mortality from RSV in developed countries is conspicuously less common.[64] US data indicate approximately 42 annual deaths in children with RSV, whereas estimates for developing countries suggest approximately 59,000 infant deaths annually are due to RSV.[8,64]

Many host, socioeconomic, and environmental factors have been associated with a greater likelihood of young children developing more severe RSV infection and requiring hospitalization (see "Patients at High Risk for Severe Infection").[2,6] Population-based surveillance of RSV hospitalizations and emergency department and outpatient visits in the counties surrounding Rochester, New York; Nashville, Tennessee; and Cincinnati, Ohio, during 2000 to 2004 indicated that outpatient visits constituted a major proportion of the health care burden attributable to RSV.[3] Of all visits for acute respiratory illnesses (ARI) among children within the first 5 years of life, RSV infection was documented among 20% of ARI hospitalizations, 18% of emergency department ARI visits, and 15% of office ARI visits. Estimated rates of ARI visits from RSV among children younger than 5 years in pediatric practices (80 per 1000 children) were approximately 3 times that observed among emergency department patients and 26 times hospitalization rates.

Fewer data exist on the health care burden imposed by RSV infection among older children and adults.[58,65] In the Houston family study of children followed from birth, the infection rate was 68.8 per 100 children in the first year of life, and at least half were reinfected during the second year of life.[52] In urban Rochester, 44% of families with young children became infected with RSV during winter months when RSV was prevalent.[54] Of exposed family members, 46% were infected with RSV. Although the attack rate was highest among infants, 38% to 47% of older children and adults developed RSV infection. Similar findings were noted in family studies in Finland and rural Kenya.[66,67]

The incidence of RSV infections among older adults and the resulting appreciable clinical and economic impact are increasingly recognized.[9,12,68–72] In one study spanning 4 years, rates of RSV infection ranged from 2% to 10% per year in elderly adults 65 years of age or older and in high-risk individuals with underlying cardiopulmonary disease.[9] RSV infection among elderly adults is remarkably similar to influenza infection with respect to clinical manifestations and as a cause of hospitalization.[68,73] The rate of hospitalization attributable to RSV among elderly adults ranges from 1.5 to 23 per 10,000 in various studies.

PATHOGENESIS

Infection with RSV is primarily acquired through close contact with an infected individual by direct inoculation of infectious secretions into the eyes and nose or by touching objects contaminated with infectious secretions.[37,74,75] Large-particle aerosols engendered by coughs and sneezes of an ill person may transmit RSV to others within a radius of about 3 feet. Longer-distance spread by small-particle (droplet nuclei) aerosols appears much less likely.[37] However, more recent studies found that small-particle aerosols collected in pediatric wards and clinics during RSV season contain infectious virus at relatively low levels, providing theoretical risk of transmission.[76–78]

Experimental infection occurred in adult volunteers after an incubation period of 2 to 5 days.[79–82] In naturally acquired infection, the average incubation period ranges from 2 to 8 days. In hospitalized infants with primary infection, peak nasal viral titers range from 10^1 to 10^7 plaque-forming units (pfu)/mL (mean, 10^5 pfu/mL) and decrease slowly.[83,84] Shedding duration is typically 7 to 10 days, but virus can occasionally be detected for 30 days.[85] Increased viral load has been associated with greater disease severity.[83,84,86,87]

RSV replicates in respiratory epithelium, primarily involving ciliated columnar cells, but additional cells, such as type I and II pneumocytes, may be involved.[88,89] During primary infection, lower respiratory tract infection usually is manifested as bronchiolitis, and initial pathologic findings are a lymphocytic peribronchiolar infiltration, predominantly $CD69^+$ monocytes, with edema of the walls and surrounding tissue.[88,90,91] Subsequently, the characteristic proliferation and necrosis of the epithelium of the bronchioles develop. Small airways become obstructed from sloughed epithelium and increased mucus secretion. The airway of the young infant is particularly vulnerable to any degree of inflammation because resistance to the flow of air is related inversely to the cube of the radius. Hyperinflation results from air trapping peripheral to the sites of partial occlusion. With complete obstruction, trapped air eventually is absorbed, producing characteristic multiple areas of atelectasis. Young infants are at increased risk for developing atelectasis because collateral channels that maintain alveolar expansion in the presence of airway obstruction are not yet well developed.

Infants with lower respiratory tract disease from RSV often have pathologic evidence of both pneumonia and bronchiolitis. Patients with pneumonia demonstrate an interstitial infiltration of mononuclear cells that may be accompanied by edema and necrosis that lead to alveolar filling.[88,90] Immunohistologic analysis of lungs from infants dying with RSV demonstrated lymphocyte populations expressing CD4, CD14, and CD75, but not CD8 or CD25.[90] Some histologic evidence of recovery is present in most children with bronchiolitis within the first week of illness and is marked by the beginning regeneration of the bronchiolar epithelium. However, ciliated cells may not be present for weeks.

Immunity and Pathogenesis of Disease

Much of the knowledge regarding immune responses to RSV is from in vitro studies and in animal models. In humans, the immune response is confounded by the influence of genetics, presence of maternal antibody, environmental exposures including concurrent respiratory tract microbiota, age, and the virus.[92–95] More severe disease in the youngest infants is thought to be related to decreased levels of maternally derived RSV-specific antibody as well as physical, immune, and viral factors. The severity of RSV infection in a young infant with augmented disease induced by the inactivated RSV vaccine developed in the 1960s first suggested a role of the immune response in pathogenesis of RSV in infants.[95–98]

The potential importance of the host's immune response to disease has been supported by the observation that RSV is not generally invasive or cytopathic.[95] However, one report of fatal RSV noted that RSV antigen was extensively present in pulmonary tissue, indicating abundant viral replication.[89] Cytokine production was nearly absent, and the expression of apoptosis was increased, with the conclusion that the patient had an inadequate immune response and unchecked viral replication.

Although viral load seems to correlate with disease severity in young children and adults, and disease symptoms decrease as viral load decreases, reducing viral replication by administration of neutralizing antibody to F protein has not ameliorated clinical disease in infants.[100,101] Data in murine models of RSV indicate that nonneutralizing antibodies to the centrally conserved CX3C chemokine motif of G protein can reduce inflammatory responses even after infection is established and in the absence of reduced viral load.[102–104] Whether innate or adaptive immune responses or both are enhanced or suppressed during more severe disease remains controversial.

The influence of the nasal microbiota and their distinct metabolic pathways on clinical manifestations of RSV infection has been appreciated.[105–107] It has also been recognized that RSV infection can influence the pathogenicity of *Streptococcus pneumoniae,* and RSV epidemics are associated with an increase in pneumococcal pneumonia in young children.[108] The presence of *S. pneumoniae* or *Haemophilus influenzae* increases the susceptibility and inflammatory response of airway epithelial cells in vitro.[109,110] Even in the absence of overt bacterial infection, the nasal microbiome may affect infant peripheral blood transcriptomic response to infection and is associated with illness severity.[106]

Maternally Derived Immunity

The first barrier of defense against RSV infection in infants is maternally derived RSV-specific serum antibody. Despite a relatively short half-life of 28 to 40 days, maternally derived antibodies have been correlated with protection in some, but not all, studies.[111–116] An early study noted that higher levels of cord blood neutralizing antibody were associated with reduced risk of hospitalization and were directly correlated with older age at hospitalization.[111] A similar analysis from Denmark calculated a 26% reduction in hospitalization during the first 6 months of life for every twofold increase in cord blood neutralizing antibody.[115] In addition, a study found that higher levels of antibody to prefusion-F and G proteins of RSV and neutralizing antibody were associated with less severe disease in the first few months of life.[113] Supplementing these observational studies, and perhaps the most compelling case for the beneficial effects of antibody, results from administration of RSV polyclonal or monoclonal antibody to high-risk infants have demonstrated protection against severe RSV disease.[99,117,118]

Innate Immunity

A rapid and vigorous innate immune response is initiated when infection of the infant's respiratory epithelium occurs.[95,98,119,120] Early events include RSV interaction with Toll-like receptors 2, 3, 4, and 7, which triggers secretion of inflammatory cytokines and chemokines such as interleukin (IL)-8, monocyte chemoattractant protein 1, macrophage inflammatory proteins MIP-1α and MIP-1β, RANTES (regulated on activation, normal T-cell expressed and secreted), and eotaxin with recruitment of macrophages, mononuclear cells, natural killer cells, and eosinophils.[98,121–123] RSV infection induces cellular production of innate interferons, which are counterbalanced by viral synthesis of the NS1 and NS2 proteins that are potent inhibitors of antiviral type I and III interferons (α, β, and λ).[20] An early and robust neutrophilic infiltration into the airway is correlated with a decline in viral load before the development of T-cell responses.[124–127] Dendritic cells also infiltrate the nasal mucosa early in infection and can be noted in lower airway secretions associated with a number of proinflammatory cytokines (e.g., IL-6, tumor necrosis factor-α, IL-8). Concentrations of many of these cell types as well as levels of cytokines and chemokines have been linked to clinical disease phenotypes and severity.[120] The variability in the endowed innate defense and susceptibility of the host are being increasingly correlated with polymorphisms in genes that are integral to various components of innate immunity.[94]

Adaptive Immunity

An effective immune response to RSV infection requires a fine balance of multiple components of immunity, a balance likely determined by both host and viral factors.[92,95,120] During primary infection, serum immunoglobulin M (IgM) antibody appears within several days but is transient and detectable usually only for a few weeks.[95] IgG antibody appears during the second week, peaks in the fourth week, and begins to decline after 1 to 2 months. An anamnestic response involving all three immunoglobulin classes occurs after reinfection, and after about three infections, titers reach levels similar to those in adults.

Primary and subsequent infections result in antibody production to many of the RSV proteins including the major immunoprotective surface glycoproteins F and G.[16] Both contain neutralizing epitopes, but those on the F protein are conserved between the two viral groups. The response to the variable G protein is group and genotype specific.[128] Most adults with RSV infection develop IgG responses to the centrally conserved chemokine motif of G, although their role in recovery or protection from infection or illness is not clear.[116,129]

Although young children are able to produce neutralizing antibodies directed against both the F and G proteins, neutralizing antibody responses are blunted in infants younger than 6 months of age owing to a dampening effect of maternal antibody.[130,131] In infants, antibody responses to F and G proteins mainly involve the subclasses IgG1 and IgG3. Adults respond to the G protein with both IgG1 and IgG2 subclass antibodies, and the adult response to the F protein is predominantly IgG1. After primary and recurrent infections, antibodies usually decline substantially within months. Following natural infection, 75% of adults demonstrate a fourfold or greater decrease in titer, returning to preinfection titers within 2 years in most cases.[132] Higher titers of antibody generally correlate with better resistance to infection, but no defined level of neutralizing antibody is predictive of the risk for infection, severity of illness, or recovery in children or adults.[10,111,133–135]

RSV-specific IgA antibody, produced in nasal secretions during primary and subsequent infection, is associated with protecting the upper respiratory tract from either natural infection or experimental challenge in adults and has been correlated with viral clearance in infants.[135–137] In the adult RSV challenge model, impaired induction of IgA-specific memory B cells was noted, which may account for the ease of reinfection.[138] Children with RSV infection may also produce transient specific IgE antibody responses in the respiratory tract. Higher levels of nasal RSV-specific IgE antibody and cysteinyl leukotrienes have been correlated with increased risk for more severe illness and wheezing and with later episodes of recurrent wheezing.[120,139,140]

Cell-mediated immunity is considered pivotal for clearance of virus and clinical recovery. Adults and children with deficiencies of cellular immunity have more severe disease and prolonged virus shedding.[141,142] Most data delineating the specific components of the cellular immune response induced by RSV are derived from rodent models and, to a lesser extent, from humans.[92,95,120] RSV infection has multiple inhibitory effects on the cellular immune response. Diminished in vitro lymphoproliferative responses during initial and repeated infections suggest impaired RSV-specific helper T-cell responses. Furthermore, RSV-infected dendritic cells have diminished ability to activate $CD4^+$ T cells, and enhanced apoptosis of $CD4^+$ and $CD8^+$ lymphocytes is observed among infants with bronchiolitis.[120,143,144]

The relationship between disease manifestations and the balance between Th1 and Th2 T-cell responses during infection has been an area of great interest. RSV infection in animals and humans engenders both Th1 and Th2 responses. Th1-dominant responses, characterized by the production of $CD8^+$ cytotoxic lymphocyte and Th1 $CD4^+$ cells secreting IL-2, IFN-γ, and tumor necrosis factor-α, are associated with viral clearance and minimal pulmonary cytopathology in animal models. In contrast, Th2 $CD4^+$ cells, with associated IL-4, IL-5, IL-10, and IL-13 secretion, impairs $CD8^+$ T-cell function and viral clearance.[145] An overexuberant memory $CD8^+$ T-cell response can mediate severe immunopathology in murine models of RSV infection.[146] IL-4 and IL-13 also augment isotype switching to IgE, and a Th2-biased response has been correlated with wheezing, more severe disease, and greater cellular inflammation and eosinophilia in the lung.[139]

Infants infected in the first several months of life have higher levels of Th2-type cytokines in nasal secretions than older infants.[147,148] Transcriptomic analysis of isolated circulating CD4 T cells during primary RSV infection in young infants suggested a pattern of activation consistent with a Th2 environment, including evidence of Th9 activation, that was associated with more severe disease.[149] Inactivated virus, as used in the initial formalin-inactivated vaccine and even in subunit vaccines, is more likely than live virus to induce a Th2-like response in experiments with unprimed animals.[145]

CLINICAL MANIFESTATIONS

Clinical observations have confirmed that naturally acquired immunity to RSV infection is incomplete. However, severe disease rarely occurs after primary infection in healthy children. Lower respiratory tract involvement and severe disease may occur during repeat infections but is generally confined to individuals with underlying conditions at either end of the age spectrum.[9,52,53]

Infection Among Young Children (Bronchiolitis and Other Lower Respiratory Tract Illnesses)

Primary infections frequently involve the lower respiratory tract, particularly in the first several months of life, and manifest most commonly as bronchiolitis, followed by pneumonia and tracheobronchitis.[3,52,53] Croup is uncommon, accounting for less than 2% to 10% of cases. Upper respiratory tract signs almost always accompany lower respiratory tract disease. Infection may be confined to the upper respiratory tract, which in young children is commonly associated with fever and otitis media. The first infection is rarely asymptomatic.[52–54] The risk for lower respiratory tract involvement with first infections is high; pneumonia or bronchiolitis has been estimated to occur in 30% to 71%, depending on the age and population.[3,52,53,150] Among infants younger than 6 months of age with underlying cardiopulmonary disease or in close contact with young children such as those attending child care, the proportion developing lower respiratory tract disease may be even higher.[53] Illness severity among preschool-aged children seeking outpatient care is considerable, with two-thirds manifesting wheezing and three-fourths having labored breathing.

RSV usually starts with upper respiratory tract illness with nasal congestion and cough. Hoarseness and laryngitis are not prominent features. Low-grade fever lasting 2 to 4 days occurs in most infants early in the illness. The height or duration of fever does not correlate with disease severity, and fever is frequently absent by the time of lower respiratory tract involvement. With progression to the lower respiratory tract, cough may become more prominent and productive, followed by increased respiratory rate, dyspnea, and retractions of intercostal muscles. With bronchiolitis, both expiratory and inspiratory obstruction may be evident. The infant may have crackles and wheezing on auscultation. The rapid variability in the presence and intensity of physical findings is characteristic of bronchiolitis, with marked transient swings in oxygen saturation often noted. Repeated observations are required for adequate assessment of clinical severity.[151]

Infants with lower respiratory tract infection commonly have impaired oxygenation[151]; however, hospitalization based on hypoxia alone is controversial. Mild degrees of desaturation may persist despite clinical improvement. Approximately 10% of infants who are hospitalized develop alveolar hypoventilation and hypercarbia, requiring respiratory support. Hospitalization, if required, averages 2 days, but prolonged hospitalization is not uncommon.[3] For most infants, however, the duration of the acute illness is 3 to 10 days.

Abnormalities on chest radiograph may be minimal, regardless of the severity of the child's illness. Hyperaeration is especially indicative of RSV infection and may be associated with peribronchial thickening.[152,153] Most children exhibit only airway disease. Less than 10% of bronchiolitis cases have evidence of both airway and airspace disease, and only about 1% have parenchymal consolidation.[152] Opacities are commonly misdiagnosed as bacterial pneumonia. These most common findings are subsegmental in right upper or middle lobes and result from atelectasis. Pleural fluid is rarely demonstrated.

Otitis Media

Acute otitis media is a common complication of RSV infection among young children.[154–156] Among children within the first 3 years of life who developed acute otitis media, 74% had RSV detected in middle ear fluid. Acute otitis media usually develops about 5 days after the onset of the respiratory illness and is more common among children older than 1 year. Otitis and earache are common complications even among older children and previously healthy adults with RSV infection; these complications also were noted in approximately half of hospitalized infants in one study.[54,65,156] RSV has been recovered from the middle ear fluid as the sole pathogen, with bacteria, or with another virus in 2% to 22% of cases.[154,156] The most frequent concurrent bacterial pathogens are *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis.*[156] Clinical and experimental evidence suggests that coinfection of RSV with a bacterial pathogen may prolong the duration and worsen the outcome of otitis media, resulting in a greater chance of treatment failure with antibiotics and persistent effusion.

Infections Among Older Children

The frequency of RSV infections at all ages is well illustrated among families with young children and among persons in contact with young children, as in schools and child care facilities.[52–54] Among children attending child care who had primary RSV infection in their first winter, 75% and 65% develop infection during their second and third years, respectively, using serologic and viral detection methods.[53] Recurrent infections commonly are upper respiratory tract illnesses, but 20% to 50% of recurrent infections among preschool-aged children involve the lower respiratory tract, including wheezing, although generally less severe than initial infection.[52] The overall burden of repeated infection in children younger than 5 years of age is substantial.[3]

Infections Among Adults

RSV infection in adults typically manifests with upper respiratory symptoms, nasal congestion, and scratchy throat preceding lower respiratory symptoms by several days. Wheezing is more common with RSV than with other respiratory viruses. Changes on the chest radiograph are seen in about half of hospitalized patients, with minimal lower lobe infiltrates or ground-glass appearance most common.[157] On computed tomography scan, ground-glass changes and bronchiole wall thickening are noted in 67%.[158] Adults also may have repetitive RSV infection occurring in sequential years, especially individuals living or working with children.[54,65,74,133] Despite the lack of durable immunity evoked by natural infection, both infection risk and severity of infection in adults are reduced by higher titers of serum and mucosal antibody in observational studies.[10,135]

The burden RSV places on the health care of this growing population has only recently been appreciated fully.[4,9,12,68,159–162] At greatest risk of severe illness are frail elderly patients; patients with underlying cardiopulmonary disease, especially chronic obstructive pulmonary disease; and severely immunocompromised patients.[10] Adults shed RSV at titers considerably lower than infants,[163] and thus estimates of RSV burden in this population have been hampered until more recently by lack of sensitive diagnostics. The incidence of hospitalization, found by using regression models using viral culture data from infants and adult hospital coding data, has been estimated at 86 per 100,000, or 28% of the incidence of influenza hospitalizations.[4] Using similar methods, RSV mortality in The Netherlands was 64% of that attributable to influenza.[12] Similar rates of RSV hospitalization and mortality have been reported by other authors.[120,161,164–167]

In long-term care facilities, 5% to 27% of respiratory infections have been reported to be caused by RSV, with attack rates estimated to be 1% to 15%, pneumonia rates of 10% to 20%, and mortality of 2% to 5% of infected individuals.[162] In a retrospective cohort analysis of residents of Tennessee nursing homes, RSV was associated with 15 hospitalizations, 17 deaths, and 76 antibiotic courses per 1000 people and 7% of hospitalizations and 9% of deaths from cardiopulmonary disease.[167] Among adults in daycare facilities, 10% of acute respiratory infections were due to RSV, a rate similar to influenza and coronaviruses.[159]

The highest risk for severe RSV infection is in patients with underlying cardiopulmonary disease, especially chronic obstructive pulmonary disease, and congestive heart failure.[9,68,164,168–170] The clinical illness caused by RSV in elderly adults is nonspecific and indistinguishable from other respiratory viruses, such that studies with active prospective diagnosis of RSV infection are required.[73,160] In a 4-year prospective outpatient study of 608 healthy individuals older than 65 years of age, 504 high-risk adults with cardiopulmonary conditions, and 1388 adults hospitalized with acute cardiopulmonary conditions, RSV infection was identified in 3% to 7% of the elderly cohort, 4% to 10% of the high-risk cohort, and 11% of the hospitalized cohort (Table 158.1).[9] These rates were similar to rates for influenza in the same groups. Among the hospitalized patients with RSV, 15% required intensive care and 8% died compared with 12% and 7%, respectively, of patients with influenza. In a large outpatient study of adults ≥50 years old with medically attended respiratory illness, RSV was identified in 8% compared with influenza identified in 17%.[160] The same investigators estimated the incidence of RSV medically attended respiratory illness to be 154 per 10,000, increasing with each decade of life.[11]

Peak nasal RSV titers in adults are substantially lower than in infants, ranging from 1 to 10^5 pfu/mL (mean, $10^{2.3}$ pfu/mL).[163] When simultaneously measured, virus titers in sputum are generally higher than in nasal secretions.[171] The duration of virus shedding in adults averages 10 days but can be 20 to 30 days. Higher viral load has been correlated with more severe disease.[172,173] Bacterial coinfection during RSV infection occurred in 31% of hospitalized patients, similar to the rate with influenza.[174] There are no controlled data on antiviral treatment for RSV in adults, and thus treatment is rarely considered except in immunocompromised patients (see "Therapy").

RSV severity among older adults is only partly explained by comorbidities and age-associated decline in pulmonary function, and it has been suggested that age-associated decline in immune function may be relevant. However, humoral immunity to RSV among elderly adults is equal to or greater than that among young adults.[134] In stable uninfected older adults, baseline RSV-specific $CD8^+$ T-cell function is diminished.[175–177] However, CD4 and CD8 T-cell responses during RSV infection were not age dependent, and more vigorous responses were noted in the most ill patients regardless of age.[178]

The burden of RSV among young healthy adults may be considerable and comparable to the burden influenza.[65] Among working healthy adults with RSV infection, 22% had lower respiratory tract manifestations. Compared with influenza, fever was less frequent, but earache, sinus pain, persistent productive cough, and wheezing were significantly more common with RSV (Table 158.2). In contrast to influenza, there are few descriptions of RSV infection during pregnancy or adverse impacts of maternal RSV on the fetus.[179–182] Reported rates of RSV infection in pregnant women are low (0.3–3.9/1000 person-years), but results are limited by lack of appropriate prospective viral surveillance. Severe disease with RSV during pregnancy has been reported, with one pregnant woman requiring mechanical ventilation.[182] No fetal adverse outcomes have been noted.[179]

TABLE 158.1 RSV Compared With Influenza Among Hospitalized Adults

CHARACTERISTICS	RSV (n = 132)	Influenza A (n = 144)
Age, years	76 ± 13	76 ± 12
Female sex	84 (64)	81 (56)
Chronic illness		
Any cardiac disease	71 (54)	71 (49)
Congestive heart failure	39 (30)	33 (23)
Any lung disease	77 (58)	79 (55)
Any heart or lung disease	106 (80)	113 (78)
Diabetes mellitus	35 (27)	28 (19)
Residence in long-term care facility	16 (12)	15 (10)
Smoking (current or past)	88 (67)	98 (68)
Influenza vaccination	99 (75)	98 (68)
Katz ADL score	1.2 ± 2.4	1.3 ± 3.0
IADL score	4.1 ± 4.1	3.3 ± 4.0
Length of hospital stay, days	14 ± 41	8 ± 5
Findings on chest radiography		
Infiltrate found	41 (31)	43 (30)
Congestive heart failure	17 (13)	15 (10)
Other	24 (18)	27 (19)
Admission to intensive care unit	20 (15)	17 (12)
Use of mechanical ventilation	17 (13)	15 (10)
Higher level of care at discharge than at admission	7 (5)	8 (6)
Death	10 (8)	10 (7)

[a]Values are reported as mean ± SD or number (%). Percentage may not sum to 100 because of rounding. Katz ADL score and the IADL score are functional assessments based on a 12-point scale, with 0 representing total independence and 12 representing total dependence.
ADL, Activities of daily living; *IADL,* instrumental activities of daily living; *RSV,* respiratory syncytial virus.
Modified from Falsey A, Hennessey PA, Formica MA, et al. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. *2005;352:1749–1759.*

COMPLICATIONS

Patients at High Risk for Severe Infection

Young children most likely to require hospitalization are premature infants and children with underlying chronic lung disease, cyanotic or complicated congenital heart disease, immunosuppressive conditions, or other chronic diseases that affect the handling of respiratory secretions such as neuromuscular disease.[3,117,183,184] Children with Down syndrome and other genetic diseases also are at high risk for severe disease. About one-third of children who are hospitalized with RSV infection within the first 5 years of life have one or more underlying conditions, and the proportion is greater among children older than 2 years.[3]

Preterm gestation with or without associated chronic lung disease is a major risk for severe RSV disease.[3,117,184] Hospitalization rates in infants <36 weeks of gestational age are three or more times higher than rates for full-term infants. With gestational age less than 32 weeks, the admission risk with RSV infections is increased, and the need for intensive care significantly increases. A disproportionate economic and clinical burden is contributed by late preterm infants (gestational age 33–35 weeks) with RSV infections, who represent about three-fourths of all preterm infants,[117,185] and this burden may extend into their second year.[186]

TABLE 158.2 Clinical Characteristics of Illness Caused by Influenza or RSV Among 211 Previously Healthy Adults

CHARACTERISTIC	ADULTS WITH ILLNESS CAUSED BY RSV OR INFLUENZA, NO. (%)		
	RSV (n = 177)	Influenza (n = 59)	P
Sign or symptom			
Fever (temperature >37.8°C)	50 (58)	43 (73)	< .001
Nasal congestion, rhinorrhea	157 (89)	46 (78)	< .04
Sore throat	102 (58)	32 (54)	.65
Ear pain	35 (20)	3 (5)	< .01
Headache	70 (40)	48 (81)	< .001
Sinus pain	55 (31)	8 (14)	< .01
Cough			
Nonproductive	150 (85)	47 (80)	.36
Productive	92 (52)	14 (24)	< .001
Lower respiratory tract signs, wheezing	28 (16)	5 (9)	.16
Work absence	67 (38)	39 (66)	< .001
Duration of illness, mean days (range)	9.5 (1–20)	6.8 (39–66)	< .001

RSV, Respiratory syncytial virus.
From Hall CB, Long CE, Schnabel KC. Respiratory syncytial virus infections in previously healthy working adults. Clin Infect Dis. *2001;33:792–796. Copyright © Infectious Diseases Society of America.*

Congenital heart conditions, especially cyanotic heart conditions accompanied by pulmonary hypertension, are among the top three major conditions in infants hospitalized with RSV infection; up to one-third require intensive care, and one-fifth require mechanical ventilation.[187–189] Infants hospitalized in the first few months of life with uncorrected cyanotic congenital heart disease are at particular risk, with the risk persisting beyond infancy and appearing greatest during the second year of life.[187,189] Earlier surgical correction of cardiac defects has appreciably reduced the mortality from RSV infection from 30% in the 1970s to less than 2% currently.

Multiple demographic and environmental factors have been evaluated for augmenting the risk for more severe RSV infection.[3,190,191] These factors include male sex, crowded living conditions, lower socioeconomic status, exposure to other young children in the home or child care, tobacco smoke exposure, and lack of breastfeeding. However, the degree of risk these factors contribute to expression of RSV disease in children is difficult to quantify. Two independent risk factors most consistently important for RSV hospitalization are prematurity and young age, especially within the first 3 months of life.[74,117]

The genetic background of an individual has important, but mostly undefined, effects on susceptibility to more severe disease. Certain racial and ethnic backgrounds have notably increased rates of hospitalization and severe RSV infection. Aboriginal people such as Native American Indian and Alaskan Native infants, especially those living in the Yukon-Kuskokwim Delta region, have RSV hospitalization rates three to four times that observed for other infants in the United States.[117,192] Severe disease with primary RSV infection has been correlated with specific polymorphisms in certain genetic loci affecting the immune response including expression of cytokines and inflammatory chemokines.[94]

Immunocompromised Patients

RSV is a well-recognized cause of morbidity and mortality among immunocompromised patients. Greater awareness of RSV disease in this population is a result of increasing numbers of patients undergoing solid-organ transplant (SOT) and hematopoietic cell transplantation (HCT), the use of more prolonged and intensive chemotherapy regimens, and the wider availability of sensitive diagnostic techniques for respiratory viruses.[193,194] The reported frequency of RSV infection among immunocompromised patients varies widely from about 2% to 50%, depending on the type of surveillance, the population, and the degree of immunosuppression.[142,193–200] Although rhinovirus, not RSV, is the most common respiratory virus reported following HCT or SOT, RSV is one of the most serious viral causes of morbidity and mortality in pediatric and adult SOT and HCT recipients.[201–203] Reported rates of RSV-associated complications vary widely with reports of RSV progression from upper to lower respiratory tract disease up to 55% and mortality ranging from 7% to 33% in HCT recipients, with lower rates in SOT recipients.[204]

RSV may be introduced by medical staff or individuals in the community into both inpatient and outpatient settings where immunocompromised patients receive care. Viral spread may be rapid and difficult to control and accompanied by appreciable morbidity and mortality.[142,195,197–199,205–207] The severity of RSV infection among these patients is related to the duration and degree of immunosuppression, type of transplant or immunosuppressive therapy, and other risk factors including treatment for graft-versus-host disease or organ rejection.[142,198–200,208–211] Patients with severe combined immunodeficiency states, patients with infection early after HCT, and lung transplant recipients are particularly at risk for a poor outcome. Among transplant recipients, factors associated with poor outcomes include use of bone marrow cells (in contrast to peripheral stem cells), occurrence of RSV infection before engraftment, the presence of acute or chronic graft-versus-host disease, and lymphopenia.[209] Among children, young age also is associated with a poorer prognosis.

RSV infection in these patients may clinically mimic other opportunistic agents, and the correct etiology may not be suspected. Sinusitis, otitis media, and wheezing may be more indicative of RSV infection than other respiratory pathogens; fever is not universally present. Concurrent infections by other infectious agents including community-acquired respiratory viruses may further confound or delay the diagnosis of RSV infection. In adult HCT recipients with RSV, upper respiratory tract signs precede pneumonia in 80% to 90% of patients, with progression to pneumonia in 30% to 40% after a median of 7 days.[193,194] The need for oxygen supplementation at the time of presentation is associated with significantly higher rates of respiratory failure and mortality.[211,212] With lower respiratory tract involvement, radiographic findings range from focal interstitial infiltrates, sometimes with hyperinflation or with lobar consolidation, to generalized alveolar and interstitial infiltrates, or even to a picture of acute respiratory distress syndrome.[197] With high-resolution computed tomography, the characteristic findings are airspace consolidation; small centrilobular nodules; ground-glass opacities; and thickening of the bronchial walls, which may be asymmetrical.[213]

Long-term complications in the immunocompromised host include bronchiolitis obliterans syndrome in nearly 10%, although rates of 50% can be seen in lung transplant recipients with RSV lower respiratory infection.[214] In the past, overall mortality with RSV pneumonia was reported to be up to 45%, but current mortality rates appear to be substantially less than that (15% for HCT patients with upper respiratory tract presentation; 33% for patients with lower respiratory tract disease).[212] This has been attributed to better diagnostics, prospective screening before HCT to delay transplant in the face of active RSV infection, advances in supportive care, and potentially treatment with ribavirin with or without immunoglobulin (intravenous immune globulin [IVIG] or monoclonal antibody) (see "Therapy").

Among children with human immunodeficiency virus (HIV) infection, RSV has been the most frequently identified cause of viral respiratory disease.[195] The manifestations of RSV infection vary according to the stage and severity of the HIV infection, and although most patients develop lower respiratory tract involvement, disease is generally is not as severe as disease among highly immunosuppressed transplant recipients.[215] Patients with HIV infection may shed RSV for prolonged periods. Confounding this, however, is the observation that children with HIV infection and concurrent viral respiratory infections also have a higher rate of bacterial coinfections.[215] The clinical outcome of respiratory viral infections has not been consistently different between children with and without HIV infection.

Although treatment of severely immunocompromised patients with aerosolized or even oral ribavirin is recommended by some experts, definitive guidelines are not available because of the lack of highly effective antivirals and prospective controlled trials (see "Therapy").[216,217] The most important aspect of management of immunocompromised patients is prevention of RSV nosocomial infection by strict adherence to infection control policies; guidelines for preventing opportunistic infections in hematopoietic stem cell transplant recipients are available.[193,218,219] These guidelines emphasize preventing the introduction of community respiratory viruses, including RSV, onto units with immunocompromised patients and stress the importance of early diagnosis.

Acute Complications in Infants

Apnea is one of the most striking and serious acute complications in young infants with RSV. Up to 20% of infants hospitalized with RSV infection have been admitted with apnea.[220,221] Among infants evaluated in the emergency department with bronchiolitis, 3% had a diagnosis of apnea. Infants at highest risk for apnea are preterm infants with a gestational age ≤32 weeks, infants with a history of apnea of prematurity, and infants of postnatal age of less than 44 weeks after conception. Characteristically, apnea occurs at the onset of RSV infection and may precede respiratory symptoms. The pathophysiology of apnea is unclear, although it is nonobstructive. Prognosis is generally good after acute RSV infection with no subsequent episodes, even with respiratory infections.

Infants admitted with RSV lower respiratory tract disease may be at increased risk for aspiration, which can appear clinically similar to bronchiolitis with airway hyperreactivity.[222] In a 12-month follow-up of infants hospitalized with RSV bronchiolitis, 83% developed reactive airway disease if they received neither ribavirin nor therapy for aspiration. The decrease in reactive airway episodes was greater in infants receiving ribavirin and thickened feedings than infants who received either therapy alone.

Coexistent bacterial infection is a frequent concern in infants hospitalized with RSV, and many likely receive unnecessary antibiotics. This is

due in part to young age, the presence of fever, and the relatively frequent appearance on the chest radiograph of opacities from viral infiltrates and atelectasis commonly mistaken for bacterial pneumonia. Multiple studies have shown that secondary bacterial infection is an unusual complication of RSV infection.[223–225] A 9-year prospective study identified secondary bacterial pneumonia in less than 1% of subjects, and a multicenter Spanish study identified bacteremia in only the most seriously ill children.[223,226] Furthermore, antibiotic therapy has not been shown to improve recovery from RSV lower respiratory tract disease.[227] Urinary tract infections are the most frequently identified concurrent bacterial infections.[228] In developing countries, however, respiratory bacterial coinfections are more common and may contribute appreciably to the high mortality rate from RSV. The most common coinfection in infants is infection with another virus, most commonly rhinoviruses, adenoviruses, coronaviruses, parainfluenza viruses, human metapneumovirus, and bocavirus.[229] There is no definitive evidence that viral coinfection carries a worse outcome; studies indicate that RSV coinfections may be less severe than RSV infections alone.[230,231]

Long-Term Complications

Recurrent wheezing after RSV bronchiolitis in infancy has long been recognized as a frequent sequela, but a causal link between the two remains unclear.[231a] Approximately 30% to 50% of children hospitalized with RSV infection later develop repeated occurrences of wheezing.[232–234] For many children, the severity of the recurrent wheezing episodes decreases with age, although pulmonary function abnormalities may persist in some without clinical manifestations.[235,236] Others may have persistent wheezing into adolescence or have wheezing cease during childhood and recur in adulthood. The frequency of long-term sequela in the general population is confounded by most studies having focused on children with more severe illness.

Epidemiologic evidence indicates that atopy in the child or family is not a major cause of this link. However, in a murine model of allergen-induced airway inflammation and remodeling, previous RSV infection could induce airway abnormalities in mice exposed to allergen through the airway, even though these mice had not been previously sensitized to the allergens.[237] In addition, RSV infection has been shown both in vitro and in children infected with RSV to produce an immunologic response similar to that observed with allergic sensitization, one with a predominantly Th2 T-cell profile and release of proinflammatory mediators, IgE, and neuropeptides (see "Immunity and Pathogenesis of Disease").[92,238] However, a similar response may be produced by viruses other than RSV.[239,240] Relevant to the relationship between severe RSV infection and asthma are two studies suggesting that palivizumab prophylaxis of premature infants was associated with a decrease in incidence of recurrent wheeze in the first few years of life,[241,242] although this decrease did not persist at age 6 years.[242a]

DIAGNOSIS

RSV infection in young children is most often diagnosed clinically in the setting of the community's RSV season. Clinical findings are less specific in adults, and RSV is frequently not suspected. At the present time, laboratory diagnosis is generally made by reverse-transcriptase polymerase chain reaction (RT-PCR) testing but may be made by rapid diagnostic commercial antigen tests or immunofluorescent antigen detection. Less widely available methods include culture or serologic testing. The sensitivity of viral diagnostic testing depends on the viral load and the specimen type. Nasopharyngeal washes or tracheal secretions are generally better than nasal swabs. Combined throat and nares swabs may improve the rate of recovery compared with a single nasal swab,[243,244] but sensitive RT-PCR testing methods in young children have shown similar results for RSV detection in nasal swabs alone.[245,246]

RT-PCR assay for the diagnosis of RSV infections has consistently demonstrated much higher rates of specificity and sensitivity than rapid antigen diagnostic assays and are more widely used in clinical settings due to the availability of rapid, simple commercialized laboratory test kits.[243,247] In one study of 496 specimens obtained from children with RSV infection determined by viral isolation or duplicate positive RT-PCR assays, about 50% were positive by both RT-PCR and culture, and 50% were positive by RT-PCR alone. Less than 1% were positive only by viral isolation.[244] Sensitive and specific multiplex PCR panels for 12 or more respiratory viruses are available from many manufacturers, and development of simple tests evaluating influenza and RSV simultaneously are marketed for use in point-of-care testing in outpatient and inpatient settings. In adults, RT-PCR is considerably more sensitive than rapid antigen test.[248] Serologic diagnosis is primarily useful for epidemiologic studies, especially in older adults, who have the most vigorous antibody responses to RSV.[134]

THERAPY

Most children and adults with RSV infection require no more than the usual care given to ensure comfort, fever control, and adequate fluid intake. For bronchiolitis, the most commonly administered therapies used for exacerbations of hyperreactive airway disease include hydration and supplemental oxygen, if needed. Bronchodilators and corticosteroids continue to be unnecessarily used[151,153]; multiple studies and meta-analyses have shown neither bronchodilators nor corticosteroids are effective for RSV disease or bronchiolitis of unspecified cause among previously healthy young children and are not recommended.

Antibiotic therapy for children with RSV lower respiratory tract disease should be reserved for patients with specific evidence of a coexisting bacterial infection.[151] Preemptive administration of antibiotics to children with RSV infection or bronchiolitis has not been associated with an improved outcome. Furthermore, complicating or secondary bacterial infections, other than otitis media among children with RSV infection in developed countries, is unusual.[223,224]

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), a synthetic nucleoside, is the only currently approved specific treatment for RSV lower respiratory tract disease in hospitalized infants, although it is currently used only in immunocompromised patients (see Chapter 45). The drug, administered as a small-particle aerosol, has shown modest clinical benefit and improved oxygenation in some studies, but an improvement in the duration of hospitalization or short-term outcome in infants was not consistently demonstrated.[151,249] Ribavirin has potential teratogenic properties, and precautions should be taken to guard against exposing women of potential childbearing capacity. In view of unclear benefit relative to the very high cost of aerosolized ribavirin, which more recently increased by more than 200%, ribavirin is currently reserved for the most seriously ill immunocompromised patients.[250]

Data supporting ribavirin treatment of RSV infection in severely immunocompromised patients with RSV infection is primarily drawn from retrospective case series.[142,193,251,252] In a large retrospective single-center analysis of 280 HCT patients with RSV infection, progression to lower respiratory disease and mortality was reduced significantly in patients in whom administration of inhaled ribavirin was started when symptoms were limited to the upper respiratory tract.[251] The only prospective placebo-controlled study was performed in 14 HCT patients with RSV upper respiratory tract infection, which demonstrated safety and a trend of decreasing viral load during therapy.[253] Inhaled ribavirin has been given either continuously (6 g over 18 hours per 24 hours) or intermittently (2 g over 2–3 hours three times per day). In a prospective randomized trial comparing these two dosing schedules in immunocompromised patients with RSV infection, the intermittent schedule appeared to be more effective in preventing development of lower respiratory disease.[254] The efficacy of systemic ribavirin, administered by either the oral or the intravenous route, has been reviewed in retrospective case studies of immunocompromised patients with RSV infection, with some suggestion of benefit.[255–258] Oral ribavirin also has the advantage of being able to be given to outpatients at substantially decreased cost, although concentrations of ribavirin in respiratory secretions are likely to be substantially lower than that found following aerosolized administration. Retrospective evaluation of oral ribavirin has been reported in multiple patient populations including HCT and lung transplant recipients.[259,260]

Immunoglobulin or anti-F monoclonal antibody therapy for the treatment of RSV infection in highly immunocompromised patients is based on retrospective observational studies. More recent studies in HCT patients have demonstrated the confounding influence in retrospective analyses based on whether or not subjects required oxygen at diagnosis or type of stem cell source used for transplant

(bone marrow vs. peripheral).[261] Although some studies suggest a trend toward diminished morbidity and progression to lower respiratory tract disease with IVIG/antibody use, other studies suggest that antibody-based therapies are not independently associated with improved outcome.[a] Overall, monoclonal antibodies appear safe and well tolerated by highly immunosuppressed patients. Prophylactic administration of palivizumab to immunocompromised patients is not routinely recommended,[117] although use of this drug in outbreak settings including adult HCT units and newborn intensive care units has been reported.[264] Palivizumab is extraordinarily expensive in dosages administered to adults and is approved only for intramuscular use, further complicating its potential use in adults undergoing transplant.

Multiple approaches are being investigated to develop new antiviral therapies specific for RSV disease.[265,266] New approaches include antisense/small interfering RNA (siRNA) inhibitors and inhibitors of attachment and fusion proteins of RSV including small molecule peptide fusion inhibitors, N protein inhibitors, and RNA-dependent RNA polymerase inhibitors.[192] Oligonucleotides that interfere with viral RNA, or siRNA inhibitors, have shown some promise, with a study showing inhaled RNA interference therapy in lung transplant recipients to be safe but not resulting in a reduction of viral load or symptom scores. However, per-protocol follow-up in this prospective trial demonstrated a reduction in the development of bronchiolitis obliterans syndrome.[214,266–269] A small-molecule fusion inhibitor, presatovir (GS-5806; Gilead, Foster City, CA), administered orally, reduced symptom scores and RSV loads in nasal washes in a placebo-controlled trial in healthy adult volunteers challenged with RSV.[270] Presatovir was evaluated in placebo-controlled trials in hospitalized adults and HSCT recipients with RSV-associated lower respiratory tract disease, but study endpoints were not met, and further studies with presatovir are not being conducted.[271] Another approach is the use of nucleoside analogues, which inhibit the RSV RNA polymerase. In an RSV challenge study in healthy adults, the oral cytidine nucleoside analogue, ALS-008176, was shown to decrease viral load and severity of symptoms compared with placebo.[269] Additional studies of orally administered ALS-008176 are underway in infants and adults infected with RSV.

TABLE 158.3 Infection Control Procedures, Both Standard Precautions and Contact Precautions, for Prevention of RSV Infection Recommended by the Centers for Disease Control and Prevention

RECOMMENDATION CATEGORY, PROCEDURE	COMMENTS
Category 1-B Recommendations[262,263]	
Hand washing	Water with soap or antibacterial agent or waterless antiseptic hand rub
Wearing gloves	Combined with hand washing before and after each glove change; may diminish self-inoculation
Wearing gowns	When direct contact with patient or patient secretions is likely
Wearing masks plus eye protection	Eyes and nose are major sites for inoculation
Housing patient in private room or in a cohort isolated from other patients	Patients with documented infection can be grouped and isolated from other patients; beds should be separated by >0.9 m
Using dedicated patient care equipment	Equipment, including toys, assigned to specific patients
Sometimes Recommended With Less or No Supporting Evidence	
Staff assigned according to patient's RSV status	Specific staff care only for patients with RSV infection
Visitor restrictions during RSV season	Some qualify by restricting young children only
Screening visitors for illness during RSV season	Visitor assessed by trained personnel or advised by use of an educational patient information list

RSV, Respiratory syncytial virus.
From Ralston SL, Lieberthal AS, Meissner HC, et al. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics *2014;134:e1474–e150; and Hall CB. Nosocomial respiratory syncytial virus infections: the "Cold War" has not ended.* Clin Infect Dis. *2000;360:588–598.*

PREVENTION

Infection Prevention

Prevention rather than treatment is the preferable goal for control of RSV infection. Avoiding infection in the home setting through interruption of the transmission of the virus is difficult and unlikely to be truly effective. In child care settings with good infection control practices in place, spread of RSV to more than 50% of children within a week has been documented.[272] Nonetheless, general precautions including good hand hygiene; use of hand-rub antiseptic products; and regular care or disinfection of contaminated tissues, stethoscopes, toys, and other objects likely to be contaminated with secretions are widely recommended in medical settings.[273,274]

On hospital wards, RSV poses a particular hazard for nosocomial spread.[74,197,275–277] Annual outbreaks occur with widespread infection among both children and adults including medical personnel who may continue to work despite upper respiratory tract signs. Considerable morbidity and mortality have been associated with nosocomial RSV infection among patients with underlying conditions, especially prematurity, cardiopulmonary disease, and immunocompromising conditions. Strict adherence to recommended guidelines is essential and cost-effective.

RSV may be spread by close contact and by direct inoculation of large droplets from the secretions of an infected person as well as by indirect spread from hands that touch infectious secretions in the environment.[74,276] Careful hand hygiene by all personnel is integral to preventing nosocomial transmission (Table 158.3). Additional procedures aimed at preventing self-inoculation include wearing of eye-nose goggles and gloves. Procedures aimed at reducing the risk for the introduction and spread of RSV to other personnel and patients include wearing gowns for close contact with infected patients, isolation or cohorting of infected patients, and use of rapid diagnostic techniques to assess symptomatic individuals. In addition, during the RSV season, staff with signs of respiratory illness should not care for high-risk patients, and visitors should be screened for respiratory illness.[74]

Prophylaxis

Prophylaxis using the passive administration of RSV-specific antibody currently is available primarily for groups most at risk for developing severe or complicated RSV disease. In high-risk children administered monthly doses of IVIG containing high levels of RSV neutralizing antibody (RSV-IVIG) or intramuscular monoclonal antibody, reduced rates of hospitalization due to RSV infection have been shown. RSV-IVIG has been replaced by palivizumab, a humanized monoclonal antibody developed from a mouse monoclonal antibody directed against a protective epitope of the RSV F protein. Immunoprophylaxis with five monthly intramuscular doses of 15 mg/kg initiated 1 month before the RSV season demonstrated a 4.4% to 5.8% absolute reduction in hospitalization rates among selected high-risk infants.[117] It has consistently been demonstrated that preterm infants born before 29 weeks' gestation are at greatest risk for hospitalization as a result of RSV infection.[117] For preterm infants born after 29 weeks' gestation who are otherwise healthy, there is no distinct cutoff at which the benefits of prophylaxis are clear. Palivizumab administration does not prevent infection with RSV but is associated with decreased clinical severity, risk for developing lower respiratory tract disease, and need for hospitalization.

At the present time, palivizumab is recommended by the American Academy of Pediatrics for a small group of infants in the first year of life who are considered to have a high risk for developing severe RSV disease.[278] Included are infants with prematurity (<29 weeks' gestation), chronic lung disease, functionally important cardiac disease that has not been surgically corrected, and chronic conditions that interfere with the handling of respiratory secretions.[117] Palivizumab is not

[a]References 197, 198, 208, 253, 262, 263.

recommended in the second year of life except for preterm children who required at least 28 days of supplemental oxygen at birth and continue to require supplemental oxygen, long-term systemic steroid therapy, or diuretic therapy within 6 months of the start of the second RSV season. Palivizumab is administered at a dose of 15 mg/kg for a maximum of 5 monthly doses during the RSV season. Prophylaxis should be discontinued in any child who experiences a breakthrough RSV hospitalization.[117]

Controversy exists concerning the extent of the use of palivizumab prophylaxis based primarily on concern regarding its considerable cost relative to its benefit. Economic analyses in general have not shown an overall savings in health care costs for prophylaxis of all infants less than 32 weeks' gestation and with underlying high-risk conditions, but the benefit relative to the cost among those at highest risk increases.[279,280] Mathematical modeling has suggested that four monthly doses of palivizumab initiated later in the season could provide comparable protection to five doses and improve cost-effectiveness.[281] Although the mortality from RSV infection even among high-risk infants in the United States is very low, studies evaluating the impact of decreased palivizumab administration in infants >29 weeks' gestation have demonstrated increased rates of hospital admission in infants 29 to 34 weeks' gestation and demonstrated increased morbidity as well as mortality.[282,283] The effect of palivizumab on the long-term sequelae of RSV infection has not been adequately evaluated.[241,242,284]

Children with severe immunodeficiencies may benefit from RSV prophylaxis, particularly when used early in life to prevent pretransplant infections. The use of palivizumab during or after transplant remains controversial. Using a decision analysis model to evaluate palivizumab prophylaxis to prevent RSV mortality after HCT in children, the survival rate was estimated to increase by 10%, and 12 children would need to be treated to prevent one fatal RSV infection.[264]

Additional products have been and are being evaluated for the prevention of RSV disease in high-risk individuals. The enhanced potency humanized monoclonal antibody against the F protein, motavizumab, had a 20-fold higher rate in RSV neutralization compared with palivizumab and prevented RSV disease in preterm infants, but this agent was not licensed due to safety issues (primarily rash reactions).[285,286] A trial of motavizumab in healthy Native American infants demonstrated an 87% relative reduction in hospitalizations for RSV,[287]marking the first time an anti-RSV antibody prevented serious RSV disease in healthy term infants. A new potent monoclonal antibody, MEDI18897, also known as nirsevimab, has an active site directed against the prefusion form of the RSV F protein and has approximately 100-fold potency in vitro compared with palivizumab.[288,289] This antibody is a totally human recombinant IgG1 κ monoclonal antibody with an extended half-life due to a 3–amino acid mutation in the Fc region enhancing binding within the lysosome and preventing antibody degradation and increasing recirculation to the cell surface. Safety and tolerability in adults has been established, and this compound is in clinical trials in infants.[290,291] The increased half-life may potentially provide passive protection for infants throughout an entire RSV season following a single intramuscular injection. This compound is intended for use in healthy term and at-risk preterm infants entering their first RSV season in both developed and developing countries.

Immunization

No effective vaccine for prevention of RSV in any population is available. Challenges in vaccine development include concern that an unpredictable abnormal immune-mediated response to subsequent infection could occur, such as was observed during the trials with the initial formalin-inactivated RSV vaccine.[96] Advances in molecular technology have resulted in new RSV vaccine candidates including subunit, particle, vector-based, and live-attenuated/chimeric vaccines. Recent crystallographic characterization of the RSV F-protein has led to design of a structure-based vaccine consisting of a stable prefusion form of the F-protein. This immunogen induces high levels of neutralizing antibody in mice, hamsters, and macaques and is a promising vaccine candidate.[289]

Multiple approaches are being pursued for vaccines to protect two major groups at highest risk for severe RSV disease: very young infants and frail elderly adults.[292,293] Immunization for infants would optimally be initiated within the first weeks of life because most hospitalization for RSV occurs in the first several months of life. Another approach for protection of infants is maternal immunization with a subunit vaccine, similar to the approach taken with influenza virus and tetanus.[294,295] Boosting of maternal neutralizing antibodies using the RSV F protein could potentially reduce the severity of infection in the first few months of life or delay infection until the infant is older when disease is less severe.[296,297] A large international clinical trial with a nanoparticle F protein vaccine candidate given to pregnant women at 32 to 36 weeks of gestation is underway (Novavax, Gaithersburg, MD). Infants with decreased transplacental antibody transfer such as premature infants or infants born to mothers with decreased maternal antibody transfer due to HIV infection or maternal hypergammaglobulinemia would benefit less from this strategy.[298]

An approach for older infants or children is intranasal immunization with live-attenuated vaccine strains.[299,300] The use of reverse genetics has resulted in the generation of candidate strains that contain mutations specifically chosen for their attenuating, immunogenic, and other advantageous characteristics. These candidate designer gene vaccines are potentially safer and have increased breadth of antigenic expression.[300] An advantage of this approach is that immunization should induce nasal IgA and cellular responses as well as serum antibody. An alternative approach is the use of live vectored or chimeric vaccines to deliver RSV antigens.

Subunit F or G vaccines are being considered for older adults. Several subunit F protein vaccines have been shown to be safe and immunogenic in individuals seropositive from previous natural RSV infection and should theoretically boost neutralizing serum antibodies, especially in adults, although results from several trials in elderly adults have been disappointing. Such a vaccine may also offer the possibility of boosting immunity among older children and adults who have an increased risk for developing more severe RSV infection.

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The complete reference list is available online at Expert Consult.

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159 Human Metapneumovirus

Angela R. Branche and Ann R. Falsey

SHORT VIEW SUMMARY

Definition
- Human metapneumovirus (hMPV) is a pneumovirus that causes acute respiratory tract infections.

Epidemiology
- Distribution is worldwide.
- Infection is most common in the late winter and spring in temperate climates.
- hMPV cocirculates with other seasonal viruses, including influenza and respiratory syncytial virus (RSV).
- Infection is universal by age 5 years.
- Reinfections occur throughout life.

Microbiology
- Virus is in the family Pneumoviridae, genus *Metapneumovirus;* has a nonsegmented single-stranded RNA (ssRNA).
- Diverged from avian metapneumoviruses 200 to 300 years ago.
- Two major genotypes (A and B) and four subgroups (A1, A2, B1, and B2).

Diagnosis
- Clinical syndrome is not distinct and ranges from common cold to acute respiratory distress syndrome.
- Bronchiolitis, asthma exacerbations, pneumonia occur in children.
- Diagnosis is best accomplished by reverse-transcriptase polymerase chain reaction (RT-PCR) of respiratory secretions.
- Immunofluorescence testing of respiratory secretions is less sensitive than RT-PCR but an acceptable method of diagnosis.

Therapy
- Treatment is supportive.
- Intravenous gamma globulin and ribavirin have been used in severely ill immunocompromised patients but efficacy, if any, is unclear.

Prevention
- No vaccine is available.
- Infection control measures include hand hygiene and use of masks, gowns, and gloves in outbreak situations.

Human metapneumovirus (hMPV) was isolated from the nasopharyngeal secretions collected over a 20-year period from 28 Dutch children with upper respiratory infections in the Netherlands in 2001.[1] This previously unidentified virus exhibited paramyxovirus-like morphology, and genetic analysis was most similar to respiratory syncytial virus (RSV). Serologic analyses indicate that infection with hMPV is nearly universal by age 5 years, and numerous studies show that hMPV can cause lower respiratory tract infections (LRTIs) resulting in substantial morbidity and cost.[2]

VIROLOGY

hMPV is a nonsegmented, single-stranded, negative-sense RNA virus belonging to the order Mononegavirales, family Pneumoviridae, genus *Metapneumovirus*.[1,3] hMPV particles are pleomorphic, spherical, or filamentous with a lipid envelope and projections on the surface as imaged by electron microscopy (Fig. 159.1).[1,4] Within the family Pneumoviridae are the genera *Orthopneumovirus* and *Metapneumovirus*.[5] Members of the *Orthopneumovirus* genus include human RSV and a number of animal pathogens, such as bovine, ovine, and caprine RSVs, and the pneumonia virus of mice. Until 2001, the only member of the *Metapneumovirus* genus was avian pneumovirus (APV), also known as *turkey rhinotracheitis virus. Orthopneumovirus* and *Metapneumovirus* were categorized into separate genera because of different gene numbers and order and because the viruses shared only 40% homology.

The original genetic analysis of hMPV by van den Hoogen and colleagues indicated a gene order of 3′-*N-P-M-F-M2-SH-G-L*-5′.[1] These eight genes encode for nine proteins and include nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), transcription elongation factor (M2-1), RNA synthesis regulatory factor (M2-2), small hydrophobic protein (SH), glycoprotein (G), and major polymerase subunit (L).[6] The lipid envelope of the virus is covered at the interior by the M protein and contains three surface glycoproteins (F, SH, and G) that form spikes of 13 to17 mm. Within the envelope lays a helical ribonucleoprotein complex, consisting of N, P, and L proteins and the hMPV genome.[7] The F protein of hMPV is a trimeric, type I membrane glycoprotein and serves both to bind cellular receptors and to mediate fusion.[8] Monomers of F are translated as an inactive precursor that is proteolytically cleaved by host proteases into two disulfide-linked subunits, F1 and F2, that remain covalently bound and create trimers of the metastable prefusion F conformation. During fusion, the F protein refolds through a series of unstable intermediates into a highly stable postfusion F conformation.[9] There is increasing evidence that multiple pathways may be involved in hMPV entry into cells, involving proteoglycan, integrin, and C-type lectin receptors as well as clathrin-mediated endocytosis.[10–13] For most hMPV strains fusion occurs at neutral pH, although a few strains demonstrate enhanced fusion at acidic pH that may be mediated by a pH sensor located on the prefusion F conformation.[7,9,14–16] The heptad repeat domain A in the F protein appears to be critical for fusogenecity, and recent work shows that cell-to-cell viral spread involves the creation of actin-mediated networks of branched cell–associated filaments.[17,18] Like RSV, the G protein of hMPV is heavily glycosylated and appears to serve similar functions in the viral life cycle. Current evidence suggests that the G protein helps tether virus particles to the cell surface and confers optimal infectivity but is not critical for viral attachment.[8] The absence of the nonstructural interferon-inhibiting genes *NS1* and *NS2* is the most striking difference between hMPV and RSV and confirmed its classification in the *Metapneumovirus* genus (Fig. 159.2).[19]

Sequence homology of *N, P, M*, and *F* genes of hMPV indicate the highest identity with APV serotype C (APV-C), one of four avian pneumovirus types.[19] Given the close relationship between hMPV and APV-C, it is speculated that the human virus originated from birds. Phylogenetic analyses of multiple hMPV gene sequences suggest that hMPV diverged from APV about 200 to 300 years ago.[20,21] Current evidence indicates that hMPV is a primary human pathogen rather than an avian pathogen that incidentally infects humans.[1,22]

Genetic variation among hMPV isolates clusters in two major genotypes (A and B) and five subgroups with two sublineages (A1, A2a, A2b, B1, and B2).[23,24] Novel sublineages with diversity in the *F* and *G*

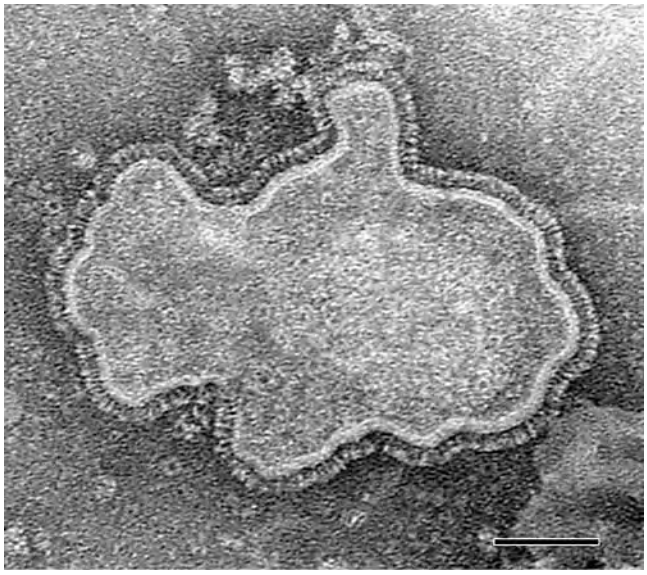

FIG. 159.1 Negative-stain electron micrograph of human metapneumovirus. This pleomorphic form of the virus is stain penetrated, thereby permitting visualization of portions of the virus envelope and nucleocapsid. A border composed of the surface projection proteins may also be seen around the virus periphery. Phosphotungstic acid negative stain, pH 6.5. Bar marker = 100 nm. *(Courtesy Charles Humphrey, PhD, research biologist, and Dean Erdman, PhD, Centers for Disease Control and Prevention.)*

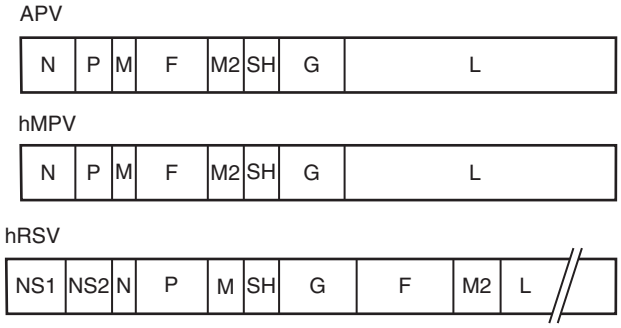

FIG. 159.2 Schematic representation of the gene order and sequence of avian pneumovirus (APV), human metapneumovirus (hMPV), and human respiratory syncytial virus (hRSV). Gene lengths are not drawn to scale.

genes have recently been described.[25,26] Isolates representing the two major genotypes have been completely sequenced, and amino acid identities between genotypes were 80% and 90%, respectively, similar to the differences found between RSV groups A and B. The greatest diversity is found in two of the surface glycoproteins, G and SH: 59% and 37% identity, respectively, which is considerably greater than the diversity observed in the RSV groups.

PATHOGENESIS AND HOST RESPONSE

hMPV infects the upper and lower respiratory tract. Type 2 alveolar and bronchiolar epithelial hMPV-infected cells have been observed in cynomolgus macaques.[7] In rodent models, hMPV replicates efficiently in the upper and lower airways with peak viral titers between days 3 and 5. Lung infection is characterized by alveolar and interstitial inflammation.[7] Limited human pathologic data indicate that bronchiolar epithelial cells are infected with hMPV, and prolonged inflammation may be observed. Bronchoalveolar lavage specimens from hMPV-infected children reveal epithelial degenerative changes, eosinophilic cytoplasmic inclusions, and multinucleated giant cells.[27] Animal data suggest that hMPV can persist in neuronal processes that innervate the lung, possibly explaining the prolonged pulmonary inflammation observed in children.[28] Lower airway involvement also occurs in adults with alveolar damage and hyaline membranes and hMPV antigens in bronchiolar epithelial cells demonstrated in autopsy samples.[29] Although hMPV and RSV are closely related viruses, the host immune responses to these two viruses are different.[7,30,31] hMPV lacks two nonstructural proteins found in RSV that are known to inhibit host interferon production, and likely uses other mechanisms to subvert innate immune responses.[32,33] In human volunteers, peripheral blood mononuclear cells stimulated with hMPV produce a stronger innate and weaker adaptive cytokine response than RSV.[34] In contrast, inflammatory cytokines measured in nasal secretions of babies infected with hMPV are less than in infants infected with RSV.[35]

Similar to RSV, immunity to hMPV is incomplete and reinfections occur throughout life in part due to poor development of T- and B-cell immunity.[36–39] The primary target of neutralizing antibody appears to be the F protein, and antibody directed against F is protective in animal models.[40] In contrast to RSV, where the most highly neutralizing antibodies are directed toward epitopes on prefusion F, pre- and postfusion hMPV F share most neutralizing epitopes.[9,41] Although serologic response is specific, several monoclonal antibodies to postfusion F neutralize both RSV and hMPV, raising the possibility of common therapeutic molecules.[41] The other surface proteins, G and SH, are weakly immunogenic and, unlike RSV, antibody to the G protein has been shown to be nonneutralizing.[42] Lymphopenia and receipt of cytotoxic therapy are risk factors for severe hMPV disease, suggesting that cellular immunity is important for hMPV illness resolution. Animal studies of CD4 and CD8 T-cell–depleted mice indicate that T cells are important for viral clearance but also contribute to disease pathogenesis.[43] Specific T-cell epitopes have been mapped to the M2 and N proteins.[7]

Because of the winter seasonality of hMPV, coinfection with other viral and bacterial respiratory pathogens ranges from 5% to 60%.[7] Several studies demonstrate that dual hMPV and RSV infection in children results in higher rates of ventilatory support, hypoxemia, and longer hospital stays, although others do not confirm these observations.[44–49] Importantly, the majority of hMPV infections are not associated with other viruses, indicating hMPV is the primary pathogen.[7] Similar to influenza, hMPV infection has been associated with bacterial pathogens such as *Streptococcus pneumoniae,* and bacterial coinfection is thought to contribute to severe disease and has been linked to increased mortality.[50–54] In children, epidemiologic studies have correlated hMPV activity with invasive pneumococcal disease, and introduction of the 7-valent pneumococcal conjugated vaccine has been shown to significantly reduce severe hMPV infections.[55,56] In one study of hospitalized adults, 39% of patients with hMPV infection had evidence of concomitant bacterial infection.[57] Animal models confirm that both influenza and hMPV predispose to severe pneumococcal infection but mechanisms of coinfection differ. The presence of the neuraminidases of influenza virus appears to promote the adherence of bacteria to the respiratory epithelium, whereas replication of hMPV is required to increase superinfection of pneumococcus in the respiratory tract.[58] In addition, hMPV infection appears to impair neutrophil recruitment to the airways, leading to delayed bacterial clearance.[59]

EPIDEMIOLOGY

hMPV is a ubiquitous pathogen that affects all age groups.[1,36,50,60] Seroprevalence studies indicate that by age 5 years, most children have been infected with hMPV. Illness caused by both RSV and hMPV appears to be common in young children, but primary infection with hMPV occurs at a slightly older age.[61,62] hMPV accounts for 2% to 3% of all symptomatic respiratory infections among children in the first 5 years of life.[60–66] In the United States, annual hospitalization rates are 3 per 1000 children younger than 6 months of age, 2 per 1000 children 6 to 11 months of age, and 1 per 1000 children younger than 5 years of age, resulting in approximately 20,000 to 27,000 yearly hospitalizations in children younger than 18 years of age.[2,60] As a cause of LRTI in children, hMPV ranks second to RSV with disease burdens similar to influenza and parainfluenza both in developed and developing countries.[53,60,67–72] A recently conducted study of community-acquired pneumonia in three cities in the United States (Nashville, TN; Memphis, TN; and Salt Lake City, UT) found that 13% of hospitalizations in children were caused

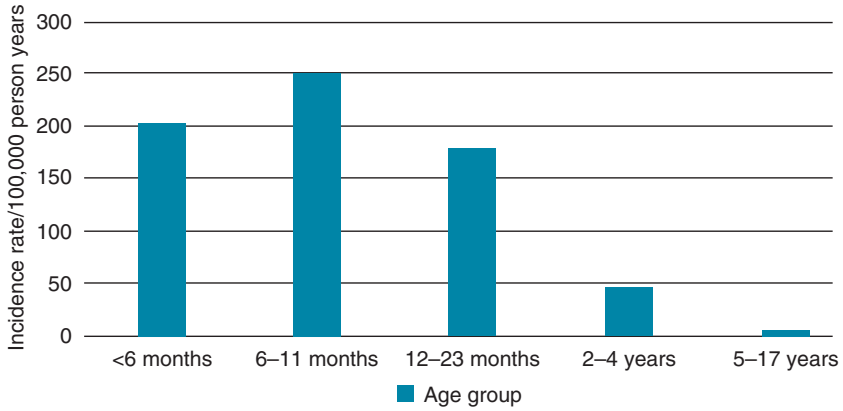

FIG. 159.3 Population-based incidence of hospitalization for human metapneumovirus (hMPV). hMPV infection rates per 100,000 person-years among children in Salt Lake City, Utah, from 2007 to 2013. *(Reproduced with permission of Journal of Pediatric Infectious Disease Society.)*

by hMPV infection.[73] A number of studies indicate that peak age for hospitalization with hMPV is somewhat older than for RSV infection, with highest rates noted between 6 and 11 months of age (Fig. 159.3).[2,60–62] hMPV also accounts for a significant number of outpatient and emergency room visits, with rates of 55 and 13 per 1000 children, respectively. Reinfection occurs throughout life, and about 2% of acute respiratory illnesses in the general adult population are due to hMPV.[36]

Numerous epidemiologic studies have now documented worldwide hMPV circulation.[1,56,61,65,74–78] In temperate climates, the virus circulates predominantly in the late winter and spring months, frequently overlapping with other seasonal respiratory pathogens and generally peaking 1 to 2 months later than RSV.[50,64,79,80] However, low levels of hMPV activity can occur during the summer months.[66,74] In the Southern Hemisphere, hMPV circulates in the summer, and in the subtropics, peak activity is in the spring and early summer.[61] Low temperature and vapor pressure and increased wind speed are associated with increased hMPV activity.[81] Most studies spanning multiple seasons indicate variation in intensity, with some showing a fairly regular biannual pattern of alternating large and small outbreaks and others showing less regular patterns of activity.[2,36,82,83] In a 5-year study from Sweden, the average incidence of hMPV infection was 2.9% but ranged from 0.8% to 5.9% depending on the year.[64] The two major genotypes of hMPV often circulate concurrently within the same community while the prevalence of genotypes and subgroups varies significantly each year, suggesting that immune pressure may play a role in the dominant circulating genotype.[65,79,83,84]

CLINICAL MANIFESTATIONS

The clinical manifestations of hMPV infection are similar to those of RSV and range from mild upper respiratory infection to bronchiolitis and severe pneumonia requiring mechanical ventilation.[6,50,85] The spectrum of disease depends on the age and the health of the host, but most infections are symptomatic.[69,83,86] The clinical syndrome is not distinct, with fever, cough, and coryza the most common symptoms. The incubation period is not precisely known, although cases of nosocomial transmission suggest an incubation period of about 5 to 6 days.[1]

Children

Most young children with hMPV infection exhibit fever, cough, sore throat, and rhinorrhea (Table 159.1).[61,62,87,88] Fever appears to be more common with hMPV than with RSV, and febrile seizures were noted in 16% of patients with hMPV compared with 3.1% in RSV-infected children in one study.[61] Wheezing is also common, with rates ranging from 22% to 83% depending on the age group studied.[62,63] In children younger than 3 years, acute otitis media has been documented in up to 60% of infected children, and hMPV RNA can be detected in middle ear fluid in some cases.[89,90] Conjunctivitis, pharyngitis, and laryngitis all occur with variable frequencies.[62,88,91] Less common symptoms include maculopapular truncal rash and diarrhea.[61] Neurologic complications

TABLE 159.1 Comparison of Signs and Symptoms in Children with hMPV, RSV, and Influenza A

	hMPV (%)	RSV (%)	INFLUENZA A (%)
Fever	52–80	47–57	78–81
Cough	90–100	99	96
Rhinorrhea	88–92	91	84
Retraction	65–92	95	82
Wheezing	22–83	23–65	5–57
Lacrimation	25	31	31
Diarrhea	8–17	17	9–27
Vomiting	10–25	8	10

hMPV, Human metapneumovirus; *RSV,* respiratory syncytial virus.
Data compiled from references 62, 63, and 67.

such as seizures, ataxia, and encephalitis appear to be approximately 10 times more common in children with hMPV compared to those infected with RSV.[92] hMPV RNA has been identified in postmortem brain tissue and cerebrospinal fluid in some cases, and a postinfectious reactive inflammatory demyelinating process has been postulated in others.[93,94]

Laboratory findings are relatively nonspecific, with lymphopenia and elevated hepatic transaminase values described.[61] Hypoxia and radiographic changes are common in hMPV-infected children, and abnormal chest radiographs have been found in 26% to 87% of hospitalized children.[61,88,95] Radiographic findings include perihilar infiltrates (87%), hyperinflation (69%), patchy opacities, and atelectasis (Fig. 159.4). Lobar consolidation occurs less frequently (18%) and may be due to bacterial complications.[56,95,96] Clinical diagnoses most frequently associated with hMPV hospitalization in children include bronchiolitis (47%–84%), asthma (11%–25%), and pneumonia (11%–17%).[60–62,91,97] The mean length of hospitalization for these children was 3 to 5 days.

hMPV has been strongly associated with bronchiolitis, pneumonia, and croup and has been detected in 4% to 8% of recurrent wheezing episodes.[98–100] The association of hMPV and asthma may in part depend on the age group studied. In older children, the dominant pathogen associated with asthma exacerbations was rhinovirus.[100] In contrast, in a case-controlled study of 133 children hospitalized with acute wheezing, the presence of hMPV was significant in children younger than 3 years.[101] In addition, infants hospitalized with hMPV bronchiolitis may be at increased risk for developing recurrent wheezing. In one study, hMPV bronchiolitis was associated with wheezing in 52% of patients at 2 years and 64% of patients at 5 years.[102]

LRTI during hMPV infection appears to be common, with hMPV RNA detected in 4% to 23% of children hospitalized with respiratory

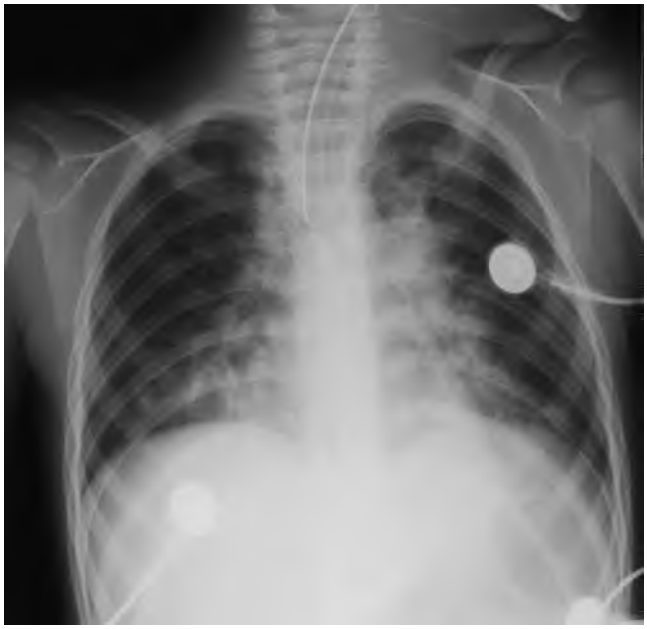

FIG. 159.4 Chest radiograph of child with human metapneumovirus (hMPV) infection. This 23-month-old child admitted to an intensive care unit required mechanical ventilation for 4 days. A chest radiograph demonstrated patchy bilateral infiltrates. Nasal wash was positive for 5.5×10^6 copies/mL of hMPV by reverse-transcriptase polymerase chain reaction. The child recovered and was discharged to home off antibiotics on hospital day 6. *(Courtesy Janet A. Englund, MD, Professor of Pediatrics, Seattle Children's Hospital, University of Washington, Seattle, WA.)*

illnesses; the highest rates were found in children younger than 3 years.[103–106] In a report of 815 children hospitalized with hMPV in Salt Lake City, Utah, 18% were treated in the intensive care unit (ICU) and 6% required mechanical ventilation, with older children more likely to require ICU care.[2] Moreover, a recent cluster of severe respiratory illnesses, including deaths in the 2 of 6 children infected with hMPV, highlights the potential severity of hMPV.[107] The majority of these children had underlying medical conditions, including premature birth, congenital heart disease, and bronchopulmonary dysplasia. Overall, prematurity confers the greatest risk for severe disease, with an odds ratio of 13.97 compared to 3.08 for RSV.[108]

In some reports, a high viral load in respiratory secretions has been correlated with disease severity, including LRTI and hospitalization in young children infected with hMPV.[109–112] There are conflicting data regarding disease severity and the role of hMPV genotypes. Several studies suggest that severity or specific symptoms may vary with genotype.[68,113] However, the bulk of current evidence indicates that severity of illness associated with hMPV A is similar to hMPV B infection.[79,110] Other risk factors for severe disease include female sex, prematurity, esophageal reflux, underlying heart and lung disease, lack of breastfeeding, vitamin D deficiency, and household crowding.[68,74,96,114]

Adults

The clinical manifestations of hMPV infection in adults, like those in children, appear to depend on age and health status. In a 4-year prospective study of respiratory illnesses in New York, hMPV was detected by serology or reverse-transcriptase polymerase chain reaction (RT-PCR) in 2.2% to 10.5% of young, healthy elderly, and high-risk adult cohorts, depending on the year.[36] Healthy adults generally present with mild influenza-like illness and common cold syndromes, with some remaining asymptomatic.[36,50,115] In addition to respiratory illnesses, a mononucleosis-like syndrome due to hMPV has also been reported.[116] Rarely, severe acute respiratory distress syndrome (ARDS) has been associated with hMPV infections in young adults without underlying disease and during pregnancy.[117–119] Recent reports also describe hMPV-associated encephalitis after influenza-like illness in adults presenting with altered mental status, headache, seizures, and either lymphocytic or mononuclear pleocytosis.[120,121] In one case, contrast magnetic resonance imaging showed bilateral subcortical and external capsule fluid-attenuated inversion recovery and diffusion-weighted imaging hyperintensities without leptomeningeal or parenchymal enhancement.[120] Finally, two cases of myopericarditis have been reported, one case in a young previously healthy 25-year-old male and a second case in a 73-year-old woman with multiple comorbidities.[122,123] Both cases were associated with pulmonary edema and echocardiography demonstrating depressed systolic ejection fraction.

With increasing age, the impact of hMPV is greater. Although healthy older adults generally do not require medical attention, wheezing and dyspnea are more common than in young adults. In contrast, adults with underlying cardiopulmonary conditions are at high risk for hospitalization where illnesses are primarily characterized by severe cough and lack of fever. It is estimated that hMPV infection accounts for 4% to 12% of COPD, 7% of asthma, and 4% of community-acquired pneumonia admissions in adults.[51,124–126] Chest radiographs revealing patchy, multilobar infiltrates associated with small pleural effusions are noted in 50% of cases.[124] In studies of patients hospitalized in New York and Tennessee, 4.5% to 8.5% of illnesses were identified as hMPV related, with those infected having high rates of chronic cardiopulmonary conditions.[36,127] In a 4-year study of 128 patients hospitalized with hMPV, 31% required ICU admission, the majority of whom also required mechanical ventilation and half of whom had ARDS.[85] Solid organ transplant recipients (20%), chronic respiratory insufficiency (13%), congestive heart failure (25%), and severe COPD (20%) were the most common underlying comorbidities. Of note, 6 patients with ARDS had only minor comorbidities. Lastly, hMPV outbreaks have been reported in long-term care facilities and may result in high rates of LRTI and death.[29,128]

Immunocompromised Hosts

As is found with other common respiratory viruses, hMPV infection can be associated with severe illness and pneumonitis in immunocompromised patients.[129–131] hMPV infections have been described in patients receiving chemotherapy, recipients of solid organ transplants, and recipients of hematopoietic stem cell transplants (HSCTs).[132–135] In patients with cancer, hematologic malignancy, nosocomial infection, and hypoxia are risk factors for LRTI.[135] Patients receiving HSCTs are at highest risk of adverse outcomes. Symptoms of hMPV infection typically begin with nasal congestion and cough but may evolve into LRTI with diffuse pneumonia and respiratory failure in one-third of cases, with reported fatality rates as high as 80% (mean, 26%–28%).[129,136] In one report of five hMPV-infected HSCT recipients, four developed rapidly progressive respiratory failure and had a septic shock–like picture with pulmonary hemorrhage.[129] Risk factors for progression to LRTI include high-dose steroid use within 2 weeks prior to diagnosis, low lymphocyte count, timing since HSCT (before day 30), nosocomial infection, and hypoxia at presentation.[136,137] No correlation has been shown between viral load and progression to LRTI. Chest radiographs most often show bilateral airspace opacities, and computed tomography scan findings consist of patchy areas of ground-glass opacification and multiple nodules.[134,138] Along with diffuse alveolar damage, smudge cell formation has been found on histopathologic examination.[139] Although severe hMPV illness is often observed in HSCT recipients, mild disease and even persistent asymptomatic shedding have also been described.[132,133,140] Bronchiolitis obliterans and allograft rejection in lung transplant recipients have been linked to hMPV infection, although this association has not been conclusively proven.[131,141] Among HIV-infected children, hMPV has been associated with higher rates of bronchospasm, bacterial complications, and mortality compared with non–HIV-infected children, although the use of antiretroviral therapy may ameliorate severity.[56,70,142]

DIAGNOSIS

The virus remained unidentified for many years because the clinical syndrome is not distinct and isolation of the virus with standard cell culture techniques is difficult. hMPV replicates slowly in cell culture, does not display hemagglutinating activity, and is relatively trypsin dependent.[1] Four methods of diagnosis are currently used: viral culture, immunofluorescence assay (IFA), RT-PCR, and serology.

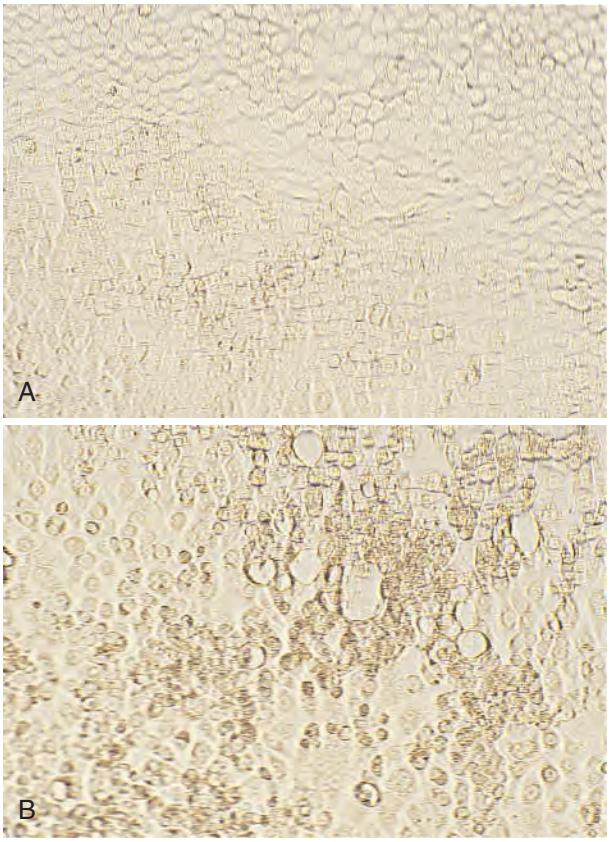

FIG. 159.5 Photomicrograph of human metapneumovirus (hMPV) (CAN97–83) in LLC-MK2 cells. LLC-MK2 cells in a semiconfluent monolayer were infected with hMPV (provided by Dr. Guy Boivan) and allowed to grow for 11 days. (A) Uninfected LLC-MK2 cells. (B) Infected LLC-MK2 cells. Granular cytopathic effects, without syncytia formation, are evident.

Viral Culture

The original isolations of hMPV were carried out on tertiary cynomolgus monkey kidney (tMK) cells or rhesus monkey kidney (LLC-MK2) cells in medium containing trypsin. Since that time a number of other cell lines have been found to support growth of hMPV, including Vero, BEAS-2B, A549, and Hep G2 cells.[7] The characteristic cytopathic effect in LLC-MK2 cells consists of small, round, granular, and refringent cells without large syncytia, and it is usually apparent after a mean of 17 days (range, 3–23 days) (Fig. 159.5).[4,50] Confirmation of hMPV infection requires either IFA with hMPV-specific antibodies or RT-PCR of the cell supernatant. Although use of shell vial cultures may speed time to identification of virus, delays in diagnosis limit clinical utility.[143]

Immunofluorescence Assay

Virus-specific monoclonal antibodies are now commercially available for direct detection of hMPV in respiratory secretions using IFA.[144,145] Although this technique is less sensitive than RT-PCR, it may be a useful alternative in microbiology laboratories that lack molecular diagnostic capabilities. Similar to RSV, rapid diagnosis of hMPV by IFA in adults may be insensitive owing to low viral load in secretions.

Reverse-Transcriptase Polymerase Chain Reaction

Because of difficulties with cell culture, molecular techniques for diagnosis of hMPV are favored as the optimal methods of diagnosis and typically use conserved regions of the *F* and *N* genes.[146,147] Detection of hMPV has been successfully incorporated into several commercially available multiplex PCR assays that simultaneously detect panels of common respiratory viruses.[148] Nasal washes and nasopharyngeal swabs are the most common respiratory samples tested, but bronchoalveolar lavage fluid and sputum can be used. Several papers suggest that, if sputum can be obtained, the yield for hMPV is higher than that of nasal secretions.[149,150]

Serology

Because seropositivity is nearly universal by age 5 years, a definitive serologic diagnosis requires a fourfold rise in antibody titer or seroconversion, and thus clinical utility is limited. Serologic diagnosis is most often accomplished by enzyme immunoassay using whole-virus lysates of the representative strains of the two major genotypes, recombinant F or N proteins as antigens, or by IFA using hMPV-infected cells fixed to slides.[6,36,151]

TREATMENT

Treatment of hMPV infection is supportive. Nebulized β-adrenergic agents, such as albuterol, have historically been administered to hospitalized children with a history of asthma or wheezing; however, current evidence suggests that this practice does not improve patient outcomes. In one recent study of children hospitalized with hMPV LRTI, the frequency of albuterol use was high (69%), although less than one-third of patients had a prior history of asthma and wheezing.[152] There were no differences in hospital length of stay or need for ICU admission between patients who received albuterol and those who did not. Similar questions regarding therapy arise in adult populations with virally induced acute exacerbation of COPD. While the benefit of bronchodilators and inhaled glucocorticoids in patients with acute exacerbation of COPD is generally accepted, one study has now demonstrated a detrimental effect of the latter therapy, whose antiinflammatory benefits may be offset by the blunting of immune responses that control viral replication.[153] Additionally, use of inhaled glucocorticoids enhanced hMPV replication in human primary bronchial epithelial cells and reduced viral apoptosis by induction of antiapoptotic genes from healthy subjects, asthmatics, and COPD patients.[153] The effect was suppressed by the use of adjuvant recombinant interferon therapy, raising potential therapeutic strategies.

Therapeutic antiviral agents or antibody preparations for the treatment or prevention of hMPV infection are not currently available but are subjects of active research[154] (see Chapter 45). Ribavirin, a nucleoside analogue with broad antiviral activity, is approved in the inhaled form for the treatment of serious RSV infections in young children (see Chapter 158). Oral ribavirin is currently licensed for the treatment of hepatitis C, and intravenous ribavirin has been administered on a compassionate-use basis for the treatment of viral hemorrhagic fevers. Polyclonal intravenous immune globulin (IVIG) was approved for the prophylaxis of RSV infections in high-risk children in 1996, although its use has been supplanted by palivizumab (see Chapter 158). Standard IVIG contains relatively high titers of neutralizing hMPV antibodies and thus may theoretically be useful for the treatment or prophylaxis of hMPV infection.[155] Ribavirin and IVIG inhibit hMPV and RSV in tissue culture and are found to have equivalent antiviral activity for both viruses.[156] In the mouse model, ribavirin combined with corticosteroid treatment was effective in reducing viral titers and histologic inflammation of the lung.[157] Ribavirin is also thought to have favorable immunomodulatory effects by upregulating CD4 and CD8 T-cell–derived interleukin-2, tumor necrosis factor-α, and interferon-γ and downregulating Th2 cytokines, thus controlling viral replication.[158] Ribavirin in various forms and IVIG have been used in seriously ill immunocompromised patients with anecdotal success.[155,159–161] Intravenous ribavirin carries a risk of intravascular hemolysis, and aerosolized ribavirin is extremely costly and can precipitate bronchospasm. An analysis using propensity scores to evaluate the effect of oral ribavirin to treat immunocompromised patients with paramyxovirus infections demonstrated no significant clinical benefit.[162] In view of lack of efficacy data and potential adverse effects, no recommendations for use of these agents have been made.[163]

hMPV-specific fusion inhibitors, humanized monoclonal antibodies, and small interfering RNAs are currently in development, and animal models indicate these agents may be useful for prophylaxis and preemptive treatment of hMPV infection.[164–169] Cross-reacting neutralizing antibodies to the RSV and hMPV fusion (F) proteins, such as MPE8 and 25P13, have been identified and may provide structural targets for

interventions.[170] DAS181 is a sialidase fusion protein that interferes with the binding of the F protein with the host cell sialic acid–containing receptor and has been explored for hMPV antiviral activity. A recent report demonstrated that DAS181 blocked hMPV infection of HEp-2 cells and inhibited binding of recombinant G attachment protein.[171] Finally, the small-molecule agent favipiravir (T-750) which is currently being evaluated for the treatment of influenza infections, has also demonstrated activity against hMPV in animal models and has broad antiviral activity.[172]

PREVENTION

Currently the major means of prevention of infection with hMPV is to interdict environmentally based or person-to-person transmission in hospital settings.

The mode of transmission of hMPV is similar to that of RSV. Efficient transmission of RSV occurs as a result of direct contact with infected secretions through fomites or large-particle aerosols. hMPV has been shown to be stable on nonporous surfaces for over 6 hours at room temperature and 4°C with minimal loss of infectivity.[173] Detection of hMPV by PCR may occur for up to 4 weeks in children with primary infection, although culture positivity is rare after 1 week.[74,83] Nosocomial transmission of hMPV has been documented in hospital settings and long-term care facilities among patients and health care workers.[37,61,91] Careful hand hygiene is of primary importance, and the use of gowns, gloves, and masks can be considered in outbreak situations.

No vaccine is currently available for the prevention of hMPV, but efforts to produce a vaccine are ongoing.[174,175] Vectored, recombinant, and chimeric vaccine candidates appear promising in small rodent and nonhuman primate models.[154,174,175] Because of concerns that inactivated vaccines may produce enhanced disease similar to RSV in immunologically naïve persons, live-attenuated vaccines are favored for development in children.[176] To date only one vaccine candidate has reached clinical trial stage; rHMPV-Pa, a live-attenuated chimeric virus vaccine candidate, was shown to replicate efficiently in vitro and be highly immunogenic in hamsters and nonhuman primates, but it proved to be overattenuated in hMPV-seronegative children in a phase I clinical trial.[177]

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The complete reference list is available online at Expert Consult.

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160 Measles Virus (Rubeola)

Anne A. Gershon

SHORT VIEW SUMMARY

Definition
- Measles is a highly contagious viral infection, usually of childhood.
- The disease presents with a nonpruritic rash that begins on the head and face and spreads down the body, with fever and malaise.
- Initially, before the rash appears, measles can resemble influenza.
- There is usually accompanying conjunctivitis, cough, and coryza.
- Complications include infections of the respiratory tract and central nervous system involvement.

Epidemiology
- Measles is very contagious before the rash appears, which enhances the chance of spread before the disease is identified.
- Measles is also contagious for a few days after rash onset.
- The virus spreads by droplets and also by the airborne route.
- Widespread vaccination with two vaccine doses in the Americas has reduced the incidence of measles so that the virus is no longer endemic in these regions.
- However, measles outbreaks continue to occur in the United States (34 outbreaks in 2013–14 and a large outbreak in 2015 related to exposure at Disneyland in California).
- When vaccination rates fall below 95%, measles outbreaks can occur if the virus is reintroduced into a population.
- Immunosuppressed patients are at high risk to develop severe measles without necessarily manifesting a rash.
- Measles vaccination has been shown to be unrelated to development of autism.

Microbiology
- Measles is caused by an RNA virus classified as a *Morbillivirus* of the Paramyxoviridae family.

Diagnosis
- Clinically, measles may be confused with Kawasaki disease.
- Measles virus is difficult to culture.
- Diagnosis is usually made clinically, particularly if Koplik spots on the oral mucosa are observed.
- Laboratory diagnosis can be made by reverse-transcriptase polymerase chain reaction on just about any body fluid or tissue.

Therapy
- No specific therapy has been proven to be useful.
- Administration of vitamin A once daily by mouth for 2 days should be considered for patients with measles.
- The mechanism of action of vitamin A is thought to be by immunomodulation.

Prevention
- Live-attenuated measles vaccine is administered to healthy children at 12 to 15 months of age and again at age 4 to 6 years.
- Passive immunization with immunoglobulin G should be given to high-risk children and adults exposed to measles but having no history of measles.

Measles, an acute infection caused by the rubeola virus, is highly contagious and usually seen in children. The illness is characterized by conjunctivitis, cough, coryza, fever, and a maculopapular rash that begins several days after the initial symptoms appear. There is a characteristic enanthem, Koplik spots, that is specific for measles and that precedes the onset of rash. Recovery from measles is the rule, but serious complications of the respiratory tract and central nervous system (CNS) may occur. Measles in the United States has been largely controlled since the introduction of live-attenuated measles vaccine in 1963; it remains a serious problem in developing countries, but successful efforts are now being carried out for improved control of the disease.[1]

Measles virus (MV) belongs to the genus *Morbillivirus* of the family Paramyxoviridae. It is closely related to the viruses causing canine and phocine distemper, rinderpest of cattle, peste des petits ruminants of goats and sheep, and morbilli of certain aquatic animals. Although these viruses are distinct agents, they share certain antigens.[2,3] Wild-type (WT) MV is pathogenic only for primates.

DESCRIPTION OF THE PATHOGEN

MV is an enveloped, nonsegmented, single-stranded, negative-sense RNA virus. The genome encodes at least eight structural proteins.[3]

Morphology

On electron microscopy measles virions are pleomorphic spheres with a diameter of 100 to 300 nm. Virions consist of an inner nucleocapsid that is a coiled helix of protein and RNA and an envelope that bears two types of short surface projections.[3,4] These projections include the hemagglutinin (H) and the fusion (F) proteins. The molecular weight of the single-stranded RNA is 4.5 kilodaltons. Because the entire genome has been sequenced, it is possible to differentiate between WT MV and vaccine-type virus.

Chemical and Antigenic Composition

MV encodes at least eight structural proteins. These have letter names and include the following: F, C, H, L (large), M (matrix), N, P, and V. Three of them, the nucleoprotein (N), the phosphopolymerase protein (P), and the large protein (L), are complexed with RNA. C and V interact with cellular proteins and also play roles in the regulation of transcription and replication of the virus. Three are associated with the viral envelope: the M protein, a nonglycosylated protein associated with the inner lipid bilayer, and the two glycoproteins, H and F.[5] The H glycoprotein is involved in attachment of the virus to host cells, and the F glycoprotein is involved in spread of the virus from one cell to another. A number of receptors for MV have been described. One is the signaling lymphocyte activation molecule (SLAM; CDw150); WT virus enters mainly using this reeceptor.[6,7,8] SLAM is a membrane glycoprotein that is expressed on T and B lymphocytes and antigen-presenting cells, which accounts for its lymphotropism and immunosuppressive effects. The complement regulatory protein CD46, which is widely distributed in primate tissues, also serves as a receptor for the MV and is particularly used by vaccine type virus.[3,9,10] A third receptor, extracellular matrix metalloproteinase inducer (CD147/EMMPRIN), on epithelial cells facilitates transmission by aerosol.[11,12] There are also additional receptors for MV. Multiple receptors probably enable MV to enter different types of cells during infection. The H glycoprotein constitutes the antigen that mediates hemagglutination. The hemagglutination inhibition (HI) test, using red

blood cells from Old World monkeys, is a historically important serologic test for measuring antibody to MV. The F glycoprotein causes hemolysis. Unlike many other paramyxoviruses, neuraminidase is not found on the envelope of MV.[13] Genetic and antigenic variations of MV are now recognized; the sequence of genes coding for H and N is the most variable.[14] Numerous genotypes have been described.[6,8,15,16] MV antigens and their role in human disease[5,17] are discussed later.

Growth of Measles Virus in Tissue Culture

MV was first successfully isolated in the laboratory by Enders and Peebles in 1954.[18] The virus was initially propagated in primary human renal cells but later was cultivated in cultured simian kidney cells. WT MV is rather difficult to propagate in vitro because it is slow growing, and only a limited number of types of cell cultures are permissive for the virus.[16] Typically, cytopathic effects produced by MV in tissue cultures consist of stellate cells with increased refractility and, especially on passage, multinucleated syncytial giant cells containing intranuclear inclusions. In the absence of cytopathic effects, virus replication can also be detected by hemadsorption of rhesus monkey erythrocytes. Presumptive isolates of MV are identified by typing with monoclonal antibodies by using immunofluorescence or plaque reduction tests.[3,19] Reverse-transcriptase polymerase chain reaction (RT-PCR) assays for MV are also available (see later).

Host Range

Humans are the only natural host for WT MV, but monkeys may also be infected. In general, illness caused by MV is milder in monkeys than that in humans.[20] It has not been possible to infect small laboratory animals, such as rodents, with WT MV. However, newborn and suckling rodents may be infected with vaccine strains administered by the intracerebral route.[21,22]

EPIDEMIOLOGY

Measles has been recognized as a disease for some 2000 years, but its infectious nature was not recognized until about 150 years ago. In 1846 Panum[23] studied an epidemic of measles in the Faroe Islands and noted that the disease was contagious, that there was an incubation period of about 2 weeks, and that infection appeared to confer lifelong immunity. The next major advance in the understanding of measles occurred in 1954, when Enders and Peebles[18] successfully propagated WT MV in primary human renal tissue culture cells. This was a prerequisite for the development of a live-attenuated measles vaccine, which was licensed for use in the United States in 1963.[24]

Measles is seen in every country in the world. Without a vaccine, epidemics of measles lasting 3 to 4 months could be predicted to occur every 2 to 5 years. Countries in which measles vaccine is widely used have experienced a marked decrease in the incidence of disease. For example, for many years, 200,000 to 500,000 cases of measles were reported annually in the United States. Since 1963, when the vaccine was licensed, the incidence of measles in the United States has decreased by almost 99%.[25,26] This decrease has been especially pronounced since the early 1980s, when state laws requiring proof of immunity to measles for school entry were enacted. The yearly incidence of measles in the United States reached its first nadir in 1983, when 1497 cases were reported to the Centers for Disease Control and Prevention (CDC) in Atlanta. In the late 1980s and early 1990s, however, there was an increase in the incidence of measles; this was brought under control by increasing the rate of immunization and by introducing a two-dose schedule of measles vaccine for all children.[27,28,29] In 1990 more than 25,000 cases of measles and 89 measles-associated deaths were reported to the CDC.[30] In 1991, however, the number of reported cases dropped significantly, to 9643.[31] Between 1993 and 1996 fewer than 1000 annual cases in the United States were reported to the CDC.[32] Between 2000 and 2007 an average of 63 annual cases were reported.[33] Since then, between 2010 and 2017 an average of about 200 cases were reported annually (range, 55–667); 2014 was a banner year, when 667 measles cases were recorded.[33a] Leaving out 2014, on average 130 measles cases were reported annually in the United States. Most cases occurred in the unvaccinated.

Using molecular techniques, it was demonstrated that transmission of indigenous measles largely ceased in the United States by 1993. Since that time most cases of measles in the United States have resulted from international importation of MV.[15]

In the first 6 months of 2008, 131 measles cases were reported to the CDC; 13% were associated with importations from Europe, Asia, and the Middle East. Of these cases, 99 (76%) were epidemiologically or virologically linked to importations. Most of these patients were younger than 20 years, and 91% were unvaccinated or had an unknown vaccination status. Of the unvaccinated individuals, many of whom declined vaccination for philosophic and/or religious reasons, 85% were eligible for vaccination. When vaccination coverage fell to 80% to 85%, measles once again became endemic in the United States. Although current vaccine coverage in the United States, which is more than 90%, is sufficient to prevent sustained outbreaks of measles, it is not sufficient to prevent imported cases, with resultant limited US spread. In the first 19 weeks of 2011, 118 cases of measles were reported to the CDC, the highest number of cases during that interval since 1996.[34] In 2011, moreover, a large epidemic of measles occurred in Quebec, Canada, with 725 reported cases, although 95% of 3-year-old children had been immunized with one dose and 90% with two doses. Among adolescents who contracted measles, 22% had received two doses. Thus, although measles vaccine is highly effective, further understanding on susceptibility in recipients of two doses is of interest.

In 2013, 11 outbreaks of measles were noted in the United States, and in 2014, 23 outbreaks were reported, including a large outbreak of 383 cases that occurred primarily among unvaccinated Amish individuals.[35] In early 2015 a multistate outbreak was noted that was related to exposure at Disney theme parks in California.[36] As of March 6, 2015, 173 cases were reported in 17 states.[35] Of the 110 cases in California, 45% were unvaccinated, and 43% had unknown or undocumented measles vaccination status. The measles isolate from this outbreak appears to be genotype B3, which has caused outbreaks in at least 14 other countries, including the Phillippines.[36] In the spring of 2017 a major outbreak of B3 measles occurred in Minnesota in a community with low vaccine coverage. There were more than 65 confirmed cases, 31% requiring hospitalization mostly for dehydration and pneumonia. Most of the cases were in infants younger than 12 months. Three children had received two doses of measles-containing vaccine. In this community the rate of measles vaccine had declined due to parental fears of measles vaccine causing autism. A major approach to control of measles in this population was to administer measles vaccine to infants younger than 1 year. For almost the past 20 years, more than half of all measles cases reported in the United States have occurred in individuals who were unvaccinated.[37,38]

Measles continues to be a worldwide problem that primarily affects children in developing countries. In 2000 it was estimated that more than 750,000 deaths attributed to measles occurred globally. With the advent of immunization programs supported by the World Health Organization and United Nations Children's Fund, the estimated deaths globally was reduced by 79% between 2000 and 2014.[39] The largest reduction in deaths was observed in Africa.[39] Measles continues to be a problem in Europe, where vaccine use may be spotty, and introduction of measles to the United States by air travel has resulted in measles outbreaks.[6,40] Despite the many challenges in controlling measles, however, eventual elimination of this infection continues to be a goal.

At present there is minimal published evidence that immunity induced by measles vaccine wanes significantly with time.[28,41–46] The major reasons why measles has not fully been eliminated from the United States are failure to immunize all persons who qualify for vaccination, primary vaccine failure, and importation of measles to the United States from other countries.[15,40–48] Based on the aforementioned recent Canadian experience, further studies on the possibility of waning immunity to measles, even after two doses, seem to be warranted.

Spread of Infection

The measles virion is very labile; it is sensitive to acid, proteolytic enzymes, strong light, and drying.[3] The virus, however, remains infective in droplet form in air for several hours, especially under conditions of low relative

humidity. This latter fact may account for the increased incidence of measles in winter.[49]

Measles is spread by direct contact with droplets from respiratory secretions of infected persons and also by the airborne route. It is one of the most communicable of the infectious diseases, most infectious during the late prodromal phase of the illness, when cough and coryza are at their peak[20]; however, the disease is probably contagious from several days before until several days after the onset of rash. MV has been isolated from respiratory secretions of patients with measles only until up to 48 hours after the onset of rash.[50] Airborne spread of measles in physicians' offices[51,52] and in a sports complex[53] has been observed.

OTHER DISEASES ASSOCIATED WITH MEASLES VIRUS

Subacute sclerosing panencephalitis (SSPE) is a chronic, degenerative, fatal neurologic disease that occurs on average 7 years after an attack of measles, particularly in children who had measles before 2 years of age. Possibly it is an autoimmune disease.[16] A few children who received measles vaccine and who had no prior history of measles have been observed to develop SSPE. It is thought that these children may have had a subclinical case of measles before receiving the vaccine. The incidence of SSPE in the United States has declined dramatically since the introduction of measles vaccine.[25,54] It is almost invariably caused by WT virus; a single case of inclusion-body encephalitis caused by the vaccine strain was reported in 1999.[55] Based on the number of cases of measles in children during 1989–91 and the number of cases of SSPE reported to the CDC after those years, it was estimated that the risk of SSPE after measles is 10 times greater than was originally thought, or 1 per 11,000 cases. Genotyping revealed that these SSPE cases were caused by the WT MV circulating during those years. It appears therefore that vaccination can prevent significantly more cases of SSPE than was originally projected.[56] More recent analysis of cases of SSPE in the current vaccine era indicate that this complication of natural measles (even mild or subclinical cases) continues to occur, underscoring the importance of measles vaccine in the US population.[57]

Patients with SSPE have unusually high measles antibody titers in their serum and their cerebrospinal fluid (CSF).[58] SSPE is caused by a persistent infection with a measles-related virus in the CNS that occurs despite a vigorous immune response on the part of the host. The pathogenesis of SSPE is extremely complex and has been ascribed to a combination of host factors and viral replicative phenomena. Although a measles-like virus has occasionally been isolated, using cocultivation techniques, from the brains of patients with SSPE at autopsy,[59,60] the infection is usually characterized by an inability to produce viral progeny.[61] This inability may be a result of defects in the formation of gene products arising from genomic mutations caused by errors of RNA replication. Originally, the inability to replicate was ascribed to failure of the infective virus to produce measles M protein.[62] Later, it was realized that this failure was related to mutations of the gene encoding this protein. Now it is recognized that defects in envelope gene products H and F also occur as a result of other genomic mutations of the causative virus. Host factors, such as defective cellular immunity and the ability of specific antibodies to confine the virus to intracellular multiplication, are also postulated to play a role in the pathogenesis of SSPE.[61–63,64–66] MV RNA was demonstrated by an in situ RT-PCR assay in neurons, astrocytes, oligodendrocytes, and vascular endothelial cells in the brain of a patient who died from SSPE.[67]

The evidence that multiple sclerosis, Crohn disease, and systemic lupus erythematosus are etiologically linked with MV is much weaker than that for SSPE,[68,69,70] and MV infection is probably unrelated to these diseases. A causative role for MV in Paget disease of bone has been raised as a possibility but as yet is unproven.[71,72,73,74]

PATHOGENESIS

MV was thought to infect by invasion of the respiratory epithelium from which it spreads to the local lymph nodes, blood, spleen, lymphatic tissue, lung, thymus, liver, and skin.[3,72,73] Recent studies in monkeys, however, have suggested that MV enters lymphoid cells of the upper respiratory tract by using the SLAM receptor. After replication in lymphoid cells, MV then invades epithelial cells in organs such as the respiratory tract, intestine, bladder, and skin. When MV infects epithelial cells, progeny are released into the airway, and thus the virus can be transmitted to new individuals.[11] Studies on volunteers inoculated with live MV have indicated that infection may occur after instillation of virus at any point from the nose to the lower parts of the respiratory tract.[71]

MV has been isolated from the leukocytes of patients with clinical measles.[75] The virus has also been propagated in vitro in human T and B lymphocytes and in monocytes.[76] The major infected cell in the blood is the monocyte.[3,77] Endothelial, epithelial, and dendritic cells are also infected. Infected tissues include the thymus, spleen, lymph nodes, liver, skin, conjunctiva, intestine, bladder, and lung.[3,6,11]

Infection of the entire respiratory mucosa accounts for the cough and coryza that are classic signs of measles. In addition, measles may directly cause croup, bronchiolitis, and pneumonia. Damage to the respiratory tract from edema and loss of cilia may predispose to secondary bacterial invasion, resulting in complications such as otitis media and pneumonia.[20]

Within a few days after generalized involvement of the respiratory tract has occurred, Koplik spots appear; subsequently rash develops. Both manifestations are believed to result from similar pathologic mechanisms. On microscopic examination of skin and mucous membranes, multinucleate giant cells and other similar histologic changes are observed in the epidermis and oral epithelium.[78] The appearance of the measles rash coincides temporally with the appearance of serum antibody and the termination of communicability of the disease. Therefore it has been postulated that the skin and mucous membrane manifestations of measles actually represent hypersensitivity of the host to the virus. MV antigen has been demonstrated in the involved skin and mucous membranes by immunofluorescence assay.[78,79,80] MV has also been isolated from the rash in its early stages.[73] If hypersensitivity is the actual cause of the rash, however, it is probably mediated by cellular rather than humoral immunity,[81] and therefore patients with agammaglobulinemia who contract measles develop a rash. Patients with deficiencies in cell-mediated immunity, on the other hand, may develop measles giant cell (Hecht) pneumonia without a rash after an exposure to measles or if measles vaccine is given.[82,83]

IMMUNITY

Immunity to measles after an attack of the disease appears to be lifelong. Rarely, second attacks of measles have been reported after natural infection. Similarly, after measles vaccination, immunity is of many years' duration and probably lifelong in most persons.[25] How measles antibody persists for years after infection is not understood. One possible explanation is that the virus becomes latent after acute infection and provides an immunologic stimulus to antibody formation. However, latent MV has not been demonstrated in humans or in experimental animals. An alternative explanation for the persistence of measles antibody is that reexposure to the virus results in persistent antigenic stimulation. Reinfection with measles can occur and is almost always asymptomatic, even though a boost in antibody titer can be detected.[84] Cellular immunity to MV probably also plays a role in the prevention of recurrent measles because patients with agammaglobulinemia do not have multiple attacks of measles. A cell-mediated response to measles antigen in the absence of detectable measles antibody was reported in two physicians in whom no disease developed despite repeated exposures to measles.[85] Therefore, when humoral antibodies to measles are absent or of low titer, cellular immunity to the virus may protect against subsequent illness. Cellular immunity to MV in peripheral blood of persons with a history of measles has been shown by in vitro lymphocyte stimulation after exposure to measles antigen[86] and by demonstration of measles-specific class I and II cytotoxic T cells.[87,88,89] A complex interplay of cellular immunity and cytokines occurs before, during, and after measles infection in healthy persons.[6,90]

During infection, CD8 and CD4 T cells are activated and probably participate in the clearance of virus and the development of rash. During recovery, suppression of cell-mediated responses occurs, with elevation of suppressive cytokines such as interleukin-4, which may be responsible for depressed delayed-type hypersensitivity to tuberculin.[3,91] Effects of

vaccine on the immune system that resemble the effects of naturally occurring measles have also been described.[92]

CLINICAL MANIFESTATIONS

The incubation period of measles is 10 to 14 days; it is often somewhat longer in adults than in children. A prodromal phase lasting several days begins after the incubation period. It is manifested by malaise, fever, anorexia, conjunctivitis, and respiratory symptoms, such as cough and coryza, and may resemble a severe upper respiratory tract infection. Measles has also been clinically confused with Kawasaki disease, especially in infants and young children. Other diseases that may mimic measles include rubella, meningococcemia, scarlet fever, toxic shock syndrome, human herpesvirus 6 and 7 infections, and parvovirus B19. Toward the end of the prodrome, just before the appearance of the rash, Koplik spots appear.

Koplik spots are pathognomonic of measles. First noted by Koplik in 1896, they consist of bluish gray specks on a red base.[93] They have been likened to grains of sand and, without examination of the buccal mucosa in good light, may be overlooked. Most often they appear on the mucosa opposite the second molars. However, in severe cases, the entire mucous membrane of the mouth may be involved. This enanthem persists for several days and begins to slough as the rash appears.

The rash of measles usually begins on the face and proceeds down the body to involve the extremities last, including the palms and soles (Fig. 160.1). During the healing phase, the involved areas (except palms and soles) may desquamate. The rash is erythematous and maculopapular; as it progresses, it becomes confluent, especially on the face and the neck. The rash usually lasts about 5 days and starts to clear first on the skin that was initially involved. The patient with measles is usually most ill during the first or second day of the rash. Several days after the appearance of the rash, the fever abates and the patient begins to feel better. The entire uncomplicated illness from late prodrome to resolution of the fever and rash lasts 7 to 10 days; cough may be the last symptom to disappear.

Complications

The most common complications of measles involve the respiratory tract and CNS. Involvement of the respiratory tract is part of the virus infection itself. In addition, bacterial superinfection may occur in any area of the respiratory tract, including the middle ear. Superinfection may be secondary to local tissue damage inflicted by the virus and depression of cellular immunity. Pneumonia accompanying measles may be caused by direct viral invasion of the lungs or by bacterial superinfection.[94] Radiographic evidence of pneumonia is common, even during apparently uncomplicated measles.[20] In infants who die of measles, pneumonia accounts for about 60% of deaths, whereas in children 10 to 14 years of age, death is more often observed to be from complications of acute encephalitis.[95,96]

Encephalitis after measles in normal hosts may be acute or chronic (e.g., SSPE). Acute measles encephalitis manifests with a resurgence of fever during convalescence and frequently with headaches, seizures, and changes in the state of consciousness. Up to 50% of patients with measles but no symptoms that suggest cerebral involvement may have abnormalities detected by electroencephalography,[97] so it is believed that viral invasion of the CNS is a common feature of measles. However, only 1 in 1000 to 2000 patients with measles develops clinical signs of encephalitis. Measles encephalitis ranges from mild to severe, and a high proportion of patients who recover are left with neurologic sequelae.

MV has been isolated from the brains of several persons dying of measles encephalitis.[98,99,100,101] However, virus isolation is uncommon and usually requires special virologic techniques such as cocultivation. It is hypothesized that acute measles encephalitis is caused by hypersensitivity to virus in brain tissue. Both viral and host antigens are present on the surface of measles-infected cells in vitro.[102] Therefore hypersensitivity may be directed against viral and host (brain) antigens, which accounts for the encephalitic symptoms. Demyelination, vascular cuffing, gliosis, and infiltration of fat-laden macrophages near blood vessel walls are noted in brain tissue from patients with measles encephalitis.[3] In a laboratory study of serum and CSF from 19 patients with postinfectious measles encephalitis, similarities between experimental allergic encephalomyelitis (e.g., immune responses to myelin basic protein, early destruction of myelin) were demonstrated in about 50%. There was no evidence of intrathecal synthesis of antibody against MV, which suggests that immunopathology, rather than viral multiplication, is involved in the pathogenesis of measles encephalitis.[103]

Transient hepatitis has also been reported during acute measles.[104]

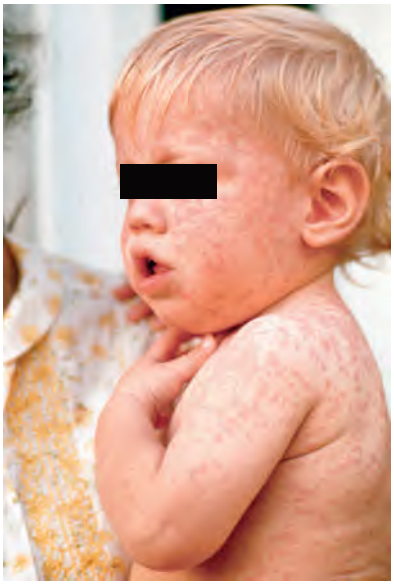

FIG. 160.1 Typical rash on a patient with measles. *(From Kremer JR, Muller CP. Measles in Europe—there is room for improvement.* Lancet. *2009;373:356–358.)*

Special Considerations

Modified Measles

An extremely mild form of measles has been observed in persons with some degree of passive immunity to the virus. This includes some babies younger than 1 year who have passively acquired maternal antibody to MV and some susceptible persons who received immune globulin after an exposure to measles. The symptoms of modified measles are variable, and certain classic symptoms, such as the prodromal period, conjunctivitis, Koplik spots, and rash, may be absent. The incubation period may be prolonged. At times the infection is subclinical and, with a great degree of passively acquired immunity, may be prevented completely.[84]

Atypical Measles

The syndrome of atypical measles has been described in persons who received killed measles vaccine (or killed vaccine, followed soon afterward by live vaccine) and who, several years later, were exposed to WT MV.[105,106] Initially, these patients have an undetectable or a very low measles antibody titer. They then develop unusual manifestations of measles, followed by the appearance of extremely high measles antibody titers (e.g., 1:100,000) in their serum.[107] After a prodrome of fever and pain for 1 to 2 days, the rash appears. Unlike classic measles, it begins peripherally and may be urticarial, maculopapular, hemorrhagic, vesicular, or some combination of these types. The disease may be misdiagnosed as varicella, Rocky Mountain spotted fever, Henoch-Schönlein purpura, drug eruption, or toxic shock syndrome. The patient has a high fever, edema of the extremities, interstitial pulmonary infiltrates, hepatitis and, on occasion, a pleural effusion. The disease tends to be severe with a somewhat more prolonged course than regular measles. At least one fatality has been reported. No specific therapy is available. MV has not been isolated from these patients, and they do not appear to transmit measles to others.[106]

The pathogenesis of this syndrome is believed to be one of hypersensitivity to MV in a partially immune host. Whether cell-mediated

or humoral immune mechanisms, or both, are involved remains controversial.[106,108,109] One hypothesis concerning pathogenesis is that killed measles vaccine lacks the antigen that stimulates the immunity that prevents entry of MV into cells, thereby allowing measles infection to occur, despite the partial immunity derived from killed vaccine.[110,111] In an animal model the low avidity of measles antibodies induced by the inactivated vaccine fails to neutralize the WT virus, leading to deposition of immune complexes, vasculitis, and pneumonitis.[3]

Recurrences of atypical measles have not been reported. Therefore those who received killed measles vaccine (or killed vaccine, followed soon afterward by live vaccine) in the past may be reimmunized with live measles vaccine. It is important that persons who have received killed vaccine be made aware, however, that severe local reactions can follow an injection of live vaccine.[112,113] Usually, the reaction consists of tenderness and erythema around the injection site. However, severe local edema and high fever may also occur. Immunization with live vaccine should be strongly considered because the associated risk is lower than the risk of being exposed to the WT virus.[114] Because killed measles vaccine was not used after 1967, atypical measles is now extremely rare.

Immunocompromised Patients

Severe measles may occur in those with compromised or deficient cellular immunity, such as those being treated for malignant disease, after transplantation, and in individuals with acquired immunodeficiency syndrome (AIDS) or any form of congenital immunodeficiency.[82,115–117] In a report of measles cases occurring in immunocompromised patients in 1989–90, combined with some recorded in the literature, the case-fatality rate for severe measles in children and young adults was calculated to be 70% in 40 oncology patients and 40% in 11 patients infected with the human immunodeficiency virus (HIV).[118] Of the oncology patients, 40% had no rash, 58% had pneumonitis, and 20% had encephalitis. Of the HIV-infected patients, 27% had no rash, and 82% had pneumonia. Should immunocompromised patients be inadvertently exposed to measles, they may develop giant cell pneumonia without evidence of a rash.[82,115,118] In such cases the clinical diagnosis of measles may be difficult or impossible to establish. Because these children may also have poor antibody responses, virus isolation from infected tissue (or identification of measles antigen by immunofluorescence) may be the only means of diagnosis. A chronic form of encephalitis resembling SSPE, often with a concomitant pneumonia, has also been reported in those with deficient cellular immunity.[63,64] This entity has been classified as subacute measles encephalitis and may be confirmed by the presence of measles RNA or infectious virus in brain tissue.[119] Even in the era of molecular diagnostic techniques, however, this diagnosis may be difficult to establish, particularly if the person had no history of clinical measles in the past.[120] Malnourished children, especially in developing countries, have also been reported to develop severe measles. This may be related to poor cell-mediated immune responses resulting from malnutrition.[121] Intense exposure to the virus because of crowding may also play a role in the severity of measles in developing countries.[122,123]

Immunocompromised patients with no history of clinical measles who are exposed to the infection should be passively immunized with immune globulin, even if they have previously been immunized (see later).

Pregnant Women and Their Offspring

Rubeola during pregnancy, in contrast to German measles (rubella), is not known to cause congenital anomalies of the fetus.[124] However, measles in pregnancy has been associated with spontaneous abortion and premature delivery.[20] Measles can be severe in pregnancy. From 1988–91, when there was a resurgence of measles in the United States, a number of pregnant women developed measles. Of 13 such women hospitalized in Houston, 54% had respiratory complications requiring admission to the intensive care unit, and one died.[125] These women were thought to have primary measles pneumonia. Measles in the offspring of mothers with measles ranges from mild to severe.[126,127] It is therefore recommended that infants born to women with active measles be passively immunized with immune globulin at birth.

Persons With Tuberculosis

It has long been thought that tuberculosis is aggravated in persons who contract natural measles, presumably because of a depression of cell-mediated immunity by MV.[3] For example, the tuberculin test has been reported to become negative for about 1 month after measles or measles vaccination.[20] It seems prudent to defer measles vaccination in persons with known tuberculosis until antituberculosis therapy is underway. In geographic areas and populations where tuberculosis is rare, it is not mandatory to perform a tuberculin test on an infant before administering measles vaccine.[128]

Occurrence in Adults

Measles has long been regarded as an illness of childhood. When it occurs in adults, it is often a more severe illness. In a series of 3220 young adult military recruits with measles between 1976 and 1979, about 3% developed pneumonia requiring hospitalization. Bacterial superinfection of the respiratory tract occurred in 30%, and 17% had evidence of bronchospasm. In addition, 31% had laboratory evidence of hepatitis, 29% had otitis media, and 25% had sinusitis.[129] In patients with measles reported to the CDC in 1991, the incidence of complications was higher in those older than 20 years than in children.[30]

DIAGNOSIS

Classic measles with cough, coryza, conjunctivitis, Koplik spots, and a maculopapular rash beginning on the face is easily diagnosed clinically. Often, there is a striking leukopenia, perhaps related to the infection and death of leukocytes. A laboratory diagnosis of measles is helpful when the clinician is unfamiliar with the illness because of the decline in cases of clinical measles since the introduction of measles vaccine. A laboratory diagnosis may also be helpful in cases of possible atypical measles or when unexplained pneumonia or encephalitis occurs in an immunocompromised patient. The differential diagnosis of measles includes rubella, Kawasaki syndrome, scarlet fever, roseola, infectious mononucleosis and rickettsial, enteroviral, and adenoviral infections.

Measles may be diagnosed in the laboratory by virus isolation, identification of measles antigen or RNA in infected tissues, or demonstration of a significant serologic response to MV. Virus isolation is technically difficult, and facilities for isolation are not always available. It is particularly useful, however, for patients with fatal pneumonia and patients with an immunodeficiency, in whom an antibody response may be minimal. Immunofluorescent examination of cells from nasal exudates or from urinary sediment for the presence of measles antigen may be useful for rapid diagnosis of measles.[124,130] A sensitive RT-PCR amplification method to demonstrate MV RNA is available, and nucleotide sequencing can be used for precise characterization of diagnostic specimens.[16,131]

A commonly used laboratory diagnostic method is the serologic response to the virus. A fourfold or greater increase in measles antibody titer in acute and convalescent serum specimens is considered diagnostic for measles. SSPE may be diagnosed by the demonstration of high measles antibody titers in serum and CSF in the presence of a compatible illness.[130] A number of methods are available for measuring antibodies to measles, usually through hospital or state health department laboratories. Neutralization, which requires propagation of the virus in vitro, is technically difficult and infrequently used. Complement fixation lacks sensitivity and is rarely used. The HI test is not used frequently today because it has been supplanted by the enzyme-linked immunosorbent assay (ELISA), for which many diagnostic kits are commercially available.

The ELISA is sensitive and simple to perform and is now widely used.[132,133] This assay can also be adapted to detect specific immunoglobulin M (IgM) antibody[134] and is therefore useful for the diagnosis of acute measles on one serum sample. False-negative and false-positive results, however, may occur with this assay. Measles IgM persists for as long as 1 month after disease onset. Antibody tests that use capillary blood collected on filter paper from finger- or heel-stick specimens have been described and are used by some state health department laboratories.[135]