Review Article

Medical Progress

Respiratory Syncytial Virus and Parainfluenza Virus

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RESPIRATORY syncytial virus (RSV), originally recovered from a colony of chimpanzees with coryza and designated chimpanzee coryza agent,[1,2] and human parainfluenza virus types 1, 2, 3, and 4 have been known primarily as respiratory pathogens in young children. They are now recognized as important pathogens in adults as well. Adults infected with these viruses tend to have more variable and less distinctive clinical findings than children, and the viral cause of the infection is often unsuspected. The consistency of the annual outbreaks of these agents and the frequency of reinfection suggest that they impose a considerable, but ill-defined, disease burden throughout life.

RSV, followed by the parainfluenza viruses, is the chief cause of hospitalization for respiratory tract illness in young children. In the 1980s an estimated 100,000 children were hospitalized with RSV infection in the United States annually, at a cost of $300 million.[3,4] In 1991 it was estimated that infection of children with parainfluenza virus types 1 and 2 accounted for 250,000 visits to emergency rooms, 70,000 hospitalizations, and $190 million annually.[5] RSV and parainfluenza viruses are also leading causes of hospitalization in adults with community-acquired respiratory disease.[6-10] Despite four decades of efforts, there are no effective means to control RSV and parainfluenza virus infections. The development of vaccines has been confounded by the lack of durable immunity, even after natural infection, and the diversity and ubiquity of populations at risk for infection.

CLASSIFICATION AND STRUCTURE

RSV and the parainfluenza viruses have many structural, pathogenic, epidemiologic, and clinical similarities. Both are enveloped RNA viruses of the family Paramyxoviridae with nonsegmented, single-stranded, negative-sense genomes.[11,12] The RSV genome encodes 10 proteins, 2 of which are nonstructural. The parainfluenza viruses possess at least one nonstructural and six structural proteins (Table 1). Integral to immunity and pathogenesis are the large envelope glycoproteins, which consist of a fusion protein (F) and a second glycoprotein. In RSV the second glycoprotein is called G, and in the parainfluenza viruses it is called hemagglutinin neuraminidase (Fig. 1). There are two major groups of RSV strains, A and B, which are distinguished mainly by variations within the G protein. There are few differences in the F protein between the A and B strains. Antigenic variations in parainfluenza viruses also occur, but they appear to be less important immunologically than the variations in RSV.[13,14]

EPIDEMIOLOGIC FEATURES

The effect of these viral infections is illustrated by their distinctive epidemiologic features (Fig. 2).[15] In the United States most RSV infections occur during a period of about 22 weeks from November to May. The peak activity in most of the country is usually in January or February and is slightly earlier in the Southeast.[15] Both the A and the B strains circulate concurrently, with the A strains usually dominating. Several distinct genotypes within these strains predominate within a community. The dominant strains shift yearly, suggesting a mechanism for frequent reinfections by evasion of immunity induced by previous strains.[16,17] The clinical severity of infections has been variably and inconclusively correlated with the strain.[11,16]

The seasonal patterns of parainfluenza virus types 1, 2, and 3 are curiously interactive (Fig. 2). Parainfluenza virus type 1 causes the largest, most defined outbreaks, marked by sharp biennial rises in cases of croup in the autumn of odd-numbered years. Outbreaks of infection with parainfluenza virus type 2, though more erratic, usually follow type 1 outbreaks. Outbreaks of parainfluenza virus type 3 infections occur yearly, mainly in spring and summer, and last longer than outbreaks of types 1 and 2. Parainfluenza virus type 4 is infrequently isolated and is therefore relatively unknown and uncharacterized. Associated illness usually is mild, but lower respiratory tract disease has been reported.[18]

PATHOGENESIS

After an incubation period of two to eight days, RSV and parainfluenza virus replicate in the nasopharyngeal epithelium, with spread to the lower respiratory tract one to three days later. The characteristic inflammation of RSV bronchiolitis is necrosis and sloughing of the epithelium of the small airways, with edema, and increased secretion of mucus, which ob-

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TABLE 1. CHARACTERISTICS OF THE PROTEINS OF RESPIRATORY SYNCYTIAL VIRUS AND PARAINFLUENZA VIRUS.

PROTEIN	MOLECULAR MASS		FUNCTIONS
	RESPIRATORY SYNCYTIAL VIRUS	PARAINFLUENZA VIRUS	
	kilodaltons		
Structural protein			
Surface			
Fusion (F)	68	60	Penetration; major protection antigen
Attachment (G)	90	—*	Viral attachment; major protective antigen
Hemagglutinin neuraminidase (HN)	—*	69	Viral attachment and release; major protective antigen
Small hydrophobic (SH [1A])	4.8–30†	—*	Unknown
Matrix			
Matrix (M)	28	40	? Mediates attachment of nucleocapsid to envelope
Small envelope (M2)	22†	—*	Transcriptional regulation; unique to pneumoviruses
Nucleocapsid-associated			
Nucleoprotein (N, NP)	44	58	Major RNA-binding nucleocapsid protein
Phosphoprotein (P)	37	60	Major phosphorylated protein; RNA-dependent RNA polymerase activity
Large polymerase complex (L)	200	250	Large nucleocapsid-associated protein; major polymerase subunit; RNA-dependent RNA polymerase activity
Nonstructural protein‡			
Nonstructural (NS1 [1C])	15.6†	—*	Function unknown; unique to pneumoviruses
Nonstructural (NS2 [1B])	14.7†	—*	Function unknown; unique to pneumoviruses

*This protein is not present in the virus.

†There are four glycosylated and nonglycosylated forms with molecular masses of 4.8, 7.5, 13 to 15, and 21 to 30 kd.

‡Nonstructural proteins are encoded variably by the different parainfluenza virus types, but all parainfluenza viruses encode at least one nonstructural protein.

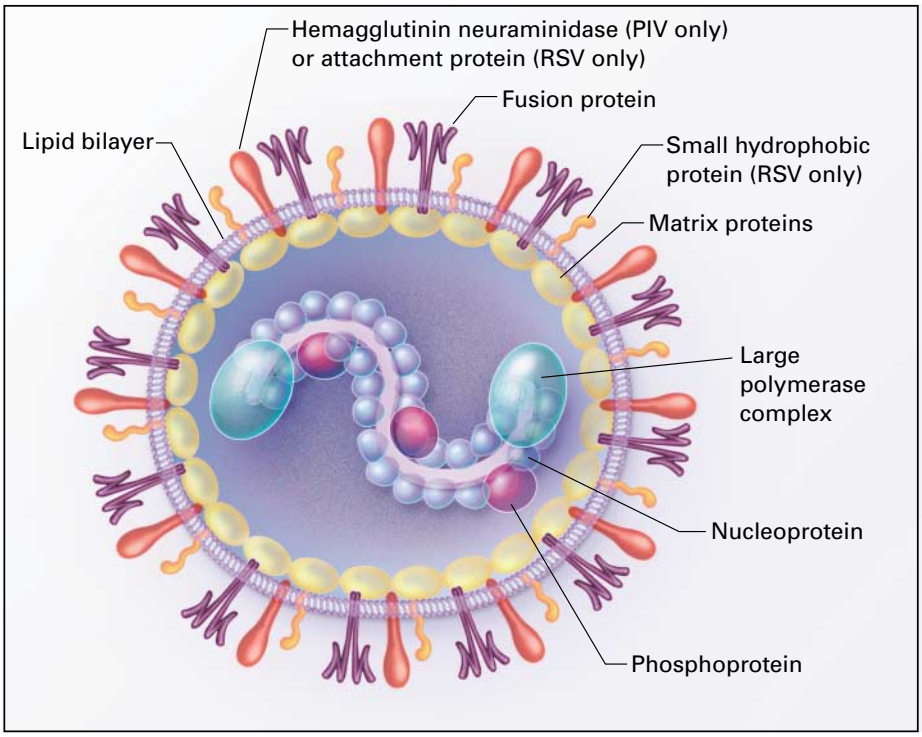

Figure 1. Structure of Respiratory Syncytial Virus (RSV) and Parainfluenza Virus (PIV).

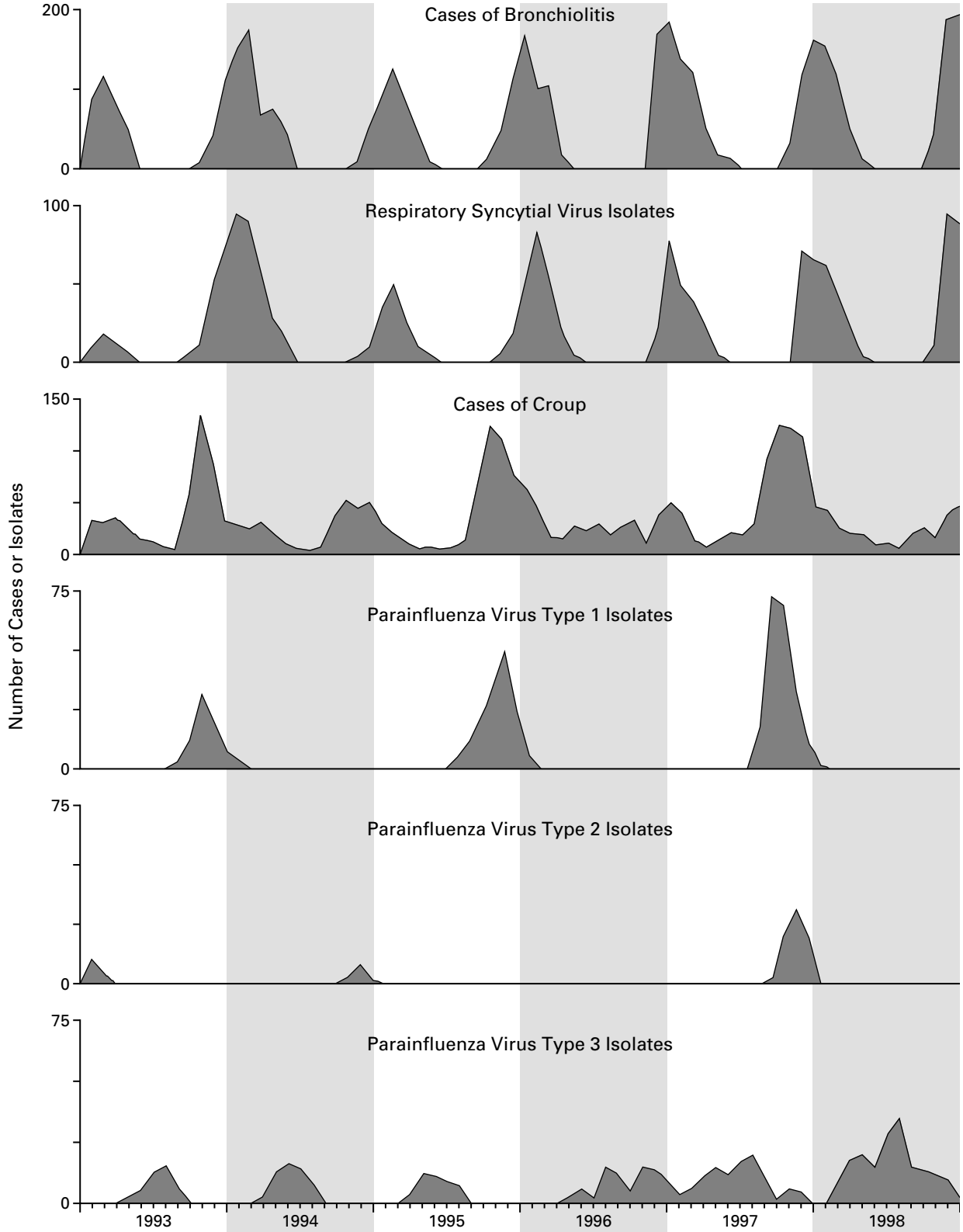

Figure 2. Epidemiologic Pattern of Infections with Respiratory Syncytial Virus and Parainfluenza Virus Types 1, 2, and 3 in Relation to the Occurrence of Bronchiolitis and Croup from 1993 through 1998.

Data were obtained from an ongoing community surveillance program in Rochester, New York. The vertical scales vary among the panels.

structs flow in the small airways (Fig. 3). The resulting clinical findings are the hallmarks of bronchiolitis: hyperinflation, atelectasis, and wheezing. Areas of pneumonia with interstitial infiltration, alveolar filling, and consolidation may predominate, especially in adults who die of the disease. Histologic evidence of recovery is apparent within days after the onset of symptoms, but ciliated epithelial cells rarely appear before two weeks. Complete restoration requires four to eight weeks, in correlation with the common clinical findings of prolonged cough, wheezing, and altered pulmonary function.[19]

Viral transmission occurs by direct inoculation of contagious secretions from the hands or by large-particle aerosols into the eyes and nose, but rarely the mouth.[20] The modes of nosocomial spread of RSV were examined by comparing rates of infection in hospital staff who had cuddled infected infants, those who had touched only contaminated toys and subsequently touched their own eyes or noses, and those who had sat close to but no more than about 1 m (3 ft) away from infected infants.[21] Those who had cuddled infants or touched toys became infected, but those who had only sat near the infants did not. This result suggests that transmission requires close or direct contact with large droplets or fomites. The prolonged survival of RSV and parainfluenza virus on skin, cloth, and other objects emphasizes the importance of fomites in nosocomial spread and of hand washing in controlling infection.[22,23]

EFFECT OF DISEASE IN CHILDREN AND ADULTS

These viruses have been primarily known as children's viruses, with good reason. Among children, RSV infection is the cause of 50 to 90 percent of hospitalizations for bronchiolitis, 5 to 40 percent of those for pneumonia, and 10 to 30 percent of those for tracheobronchitis.[24] Primary RSV infections are rarely asymptomatic.

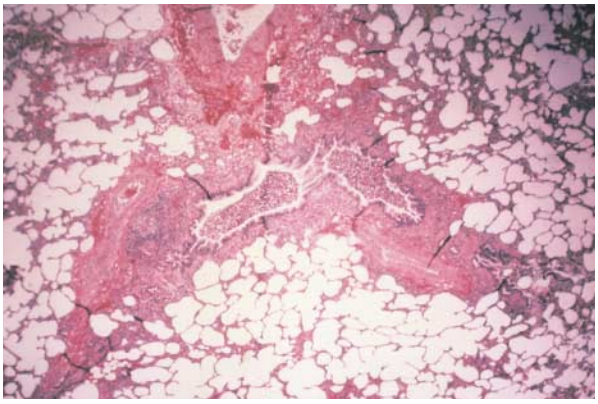

Figure 3. Bronchiolitis in an Infant with Respiratory Syncytial Virus Infection (Hematoxylin and Eosin, ×40).

Lymphocytes infiltrate the bronchiole, and sloughed necrotic material has filled and obstructed the bronchiolar lumen. The beginning of the regeneration of bronchiolar epithelium is evident.

Substantial increases in the number of admissions for RSV bronchiolitis have been documented recently in North America.[25,26] In Canada, inpatient care of RSV illness costs $18 million (U.S. dollars) yearly, accounting for 62 percent of the total cost of this disease. The magnitude of the costs is understandable, since virtually all children become infected with RSV within two years after birth, and 1 percent require hospitalization.[27] Approximately 40 percent of infants hospitalized with RSV infection in Rochester, New York, over the past 25 years had underlying conditions, most frequently low birth weight or cardiopulmonary disease.[24]

The parainfluenza viruses cause a spectrum of respiratory illnesses similar to those caused by RSV (Fig. 4), but result in fewer hospitalizations.[28,29] Most are upper respiratory tract infections, of which 30 to 50 percent are complicated by otitis media.[28,30] About 15 percent of parainfluenza virus infections involve the lower respiratory tract, and 2.8 of every 1000 children with such infections require hospitalization.[29] Most children are infected by parainfluenza virus type 3 by the age of two years and by parainfluenza virus types 1 and 2 by the age of five years. Pneumonia and bronchiolitis from parainfluenza virus type 3 infection occur primarily in the first six months of life, as is the case for RSV infection, but with a lower frequency (Fig. 5).[29] Croup is the signature clinical manifestation of infection with parainfluenza virus, especially type 1, and is the chief cause of hospitalization from parainfluenza infections in children two to six years of age.[28,31]

Infections with these viruses are much less well recognized among older populations. Recognition of reinfection with these agents in older children and adults is confounded by the fact that other respiratory agents cause similar clinical manifestations. Aggravation of an underlying condition may be the chief finding at presentation. In children with the nephrotic syndrome, RSV infection is the most frequent cause of relapses associated with upper respiratory tract infections.[32] In those with chronic pulmonary disorders, RSV and parainfluenza virus infections lead to complications that are indistinguishable from those resulting from other infectious or noninfectious causes.[33] RSV infection appears particularly detrimental in patients with cystic fibrosis, resulting in reduced lung function and a greater rate of hospitalization (43 percent) than any other viral infection.[34,35]

The current epidemic of asthma, marked by increasing severity of disease and hospitalization rates, has spotlighted the possibility of a pathogenic link between asthma and viral infections, primarily those due to RSV.[36-41] About 40 to 50 percent of infants hos-

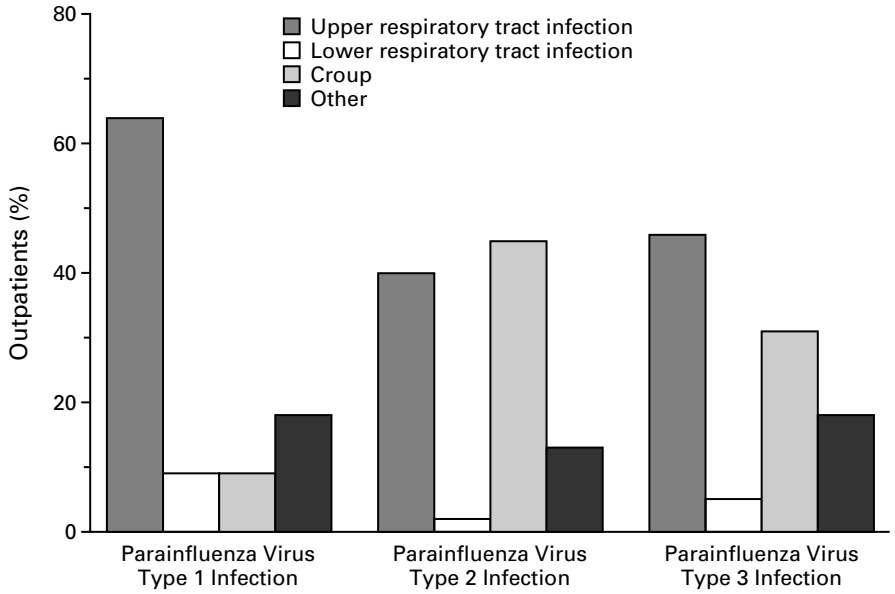

Figure 4. Clinical Syndromes Caused by the Parainfluenza Virus Types 1, 2, and 3 in Pediatric Outpatients.

Data were obtained from an ongoing community surveillance program in Rochester, New York. Upper respiratory tract infections include otitis media. Croup is defined as laryngotracheobronchitis. Other syndromes include laryngitis, tracheitis, and fever without localizing signs. Adapted from Knott et al.[28] with the permission of the publisher.

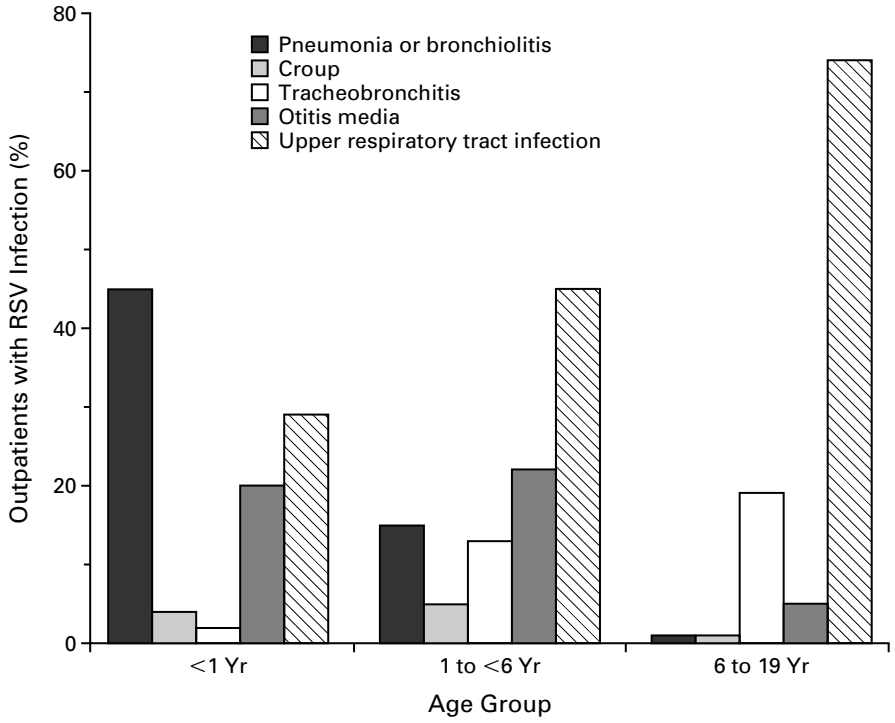

Figure 5. Incidence of Pneumonia or Bronchiolitis, Croup, Tracheobronchitis, Otitis Media, or Upper Respiratory Tract Infection among Outpatients with Respiratory Syncytial Virus (RSV) Infection, According to Age.

Data were obtained from an ongoing community surveillance program in Rochester, New York.

pitalized with RSV bronchiolitis have subsequent episodes of wheezing. Furthermore, exacerbations of asthma in children and adults are primarily associated with viral infections.[42-44] The role of respiratory viruses in wheezing is further suggested by the similarity of the inflammatory response elicited by asthmatic attacks and that elicited by viral infections. RSV infection has been associated with a T-cell response characterized primarily by the production of cytokines by type 2 helper T cells, the same response observed during episodes of asthma.[39,45] Both are characterized by the recruitment of T cells and eosinophils and the release of soluble mediators, such as histamine, kinins, and other leukotrienes.[45] Among children with bronchiolitis, more frequent and severe wheezing has been correlated with elevated levels of IgE antibody to RSV and parainfluenza virus in secretions, suggesting that virus-induced antibodies augment the release of inflammatory mediators that are important in reactive airway disease.[45] RSV may further affect wheezing by altering neural pathways that mediate airway responsiveness.[46]

Reversal of this causal link between viral infection and asthma, however, is suggested by other studies indicating that at birth the inflammatory response is normally mediated by type 2 helper T cells. This response later switches to a pattern mediated primarily by type 1 helper T cells as a result of stimulation by multiple viral infections early in life. Thus, type 1 helper T cells are selected preferentially over type 2 helper T cells, providing protection against the development of wheezing.[38] This hypothesis is supported by studies showing that children with increased levels of exposure to infections in day care or as a consequence of having multiple older siblings have an increased likelihood of frequent wheezing at the age of 2 years but a decreased likelihood of it at 6 through 13 years of age.[41]

Collectively, these studies suggest that certain respiratory viruses modulate components of the immune response, such as RSV-specific type 2 helper T memory cells, that participate in the expression of asthma-like features after multiple infectious and environmental exposures in both persons with a preexisting diathesis and those without it. Thus, these studies raise the question of whether the current epidemic of asthma could be diminished by controlling RSV and parainfluenza virus infections.

Infections in Immunocompromised Patients

The increasing number of patients who receive intense immunosuppression after undergoing transplantation of bone marrow and solid organs has highlighted the roles of RSV and the parainfluenza viruses as potential opportunistic pathogens.[47-49] These viruses are usually acquired in the community and are introduced into transplantation units by staff or visitors with mild upper respiratory tract infections. Nosocomial spread may be rapid and prolonged and may involve multiple strains introduced concurrently.[50] Infection is frequently severe, depending on the degree of immunosuppression in those affected, the type of virus, the presence or absence of other infections, and whether the infection occurs within two months after transplantation and before engraftment.[47-49,51] RSV infections tend to be more severe, with a mortality rate of 30 to 100 percent, as compared with a rate of 15 to 30 percent for parainfluenza virus.[47-49] The greater pathogenicity of RSV could be due partly to its inhibition of apoptosis, as demonstrated in vitro. Such inhibition could abet the dissemination of infection, which could be particularly devastating in immunocompromised patients.[52]

RSV and parainfluenza virus infections are often unsuspected in immunocompromised hosts, since they may mimic other opportunistic infections more commonly associated with an immunocompromised state. Furthermore, upper respiratory tract signs, if present, may appear inconsequential. Chest roentgenograms show a spectrum of findings, from focal interstitial infiltrates to lobar consolidation to diffuse alveolar–interstitial infiltrates.[47-49] Concomitant infections with other opportunistic pathogens may further confound the diagnosis and diminish the likelihood of performing additional diagnostic tests for respiratory viruses.[47,53] However, several findings tend to distinguish infections with RSV and parainfluenza virus from infections with cytomegalovirus and other opportunistic pathogens, such as the presence of upper respiratory tract signs at the onset of pneumonitis, roentgenographic evidence of sinusitis, and wheezing.

The likelihood of diagnosis is also limited by the difficulty of obtaining laboratory-based confirmation. Despite the presence of profound pulmonary abnormalities, these viruses in adults are characteristically shed in low titers, and therefore viral isolation and antigen-detection assays of upper respiratory tract specimens are insensitive as ways of establishing a diagnosis. Analysis of specimens obtained by bronchopulmonary lavage improves the yield of positive results.[47-49,54] Patients with human immunodeficiency virus (HIV) infection have prolonged shedding of RSV and parainfluenza virus, but their clinical course is generally less severe than that in transplant recipients. Although the risk of pneumonia and hospitalization is increased in HIV-infected patients, severe respiratory failure and death are uncommon.[55]

REINFECTIONS IN PREVIOUSLY HEALTHY PERSONS

The frequency of RSV and parainfluenza virus reinfections throughout life indicates that a large susceptible population is consistently available and that these usually mild reinfections are the primary source of serious infections in infants and those with underlying medical conditions. Furthermore, recent evidence

suggests that reinfections in previously healthy persons result in a considerable burden of disease requiring medical attention.

In one study in North Carolina, 98 percent of children attending day care during their first year of life became infected with RSV, 74 percent were reinfected during their second year, and 65 percent during their third year.[56] Similarly, in another study 69 percent of children in Houston acquired RSV infection during their first year, 83 percent were reinfected during their second year, and 46 percent were reinfected during their third year.[57] At least two thirds of these children were infected by parainfluenza virus type 3 in each of their first two years of life.[58] Clinical illness more frequently accompanied RSV reinfections than parainfluenza virus reinfections and was three to four times as likely to involve the lower respiratory tract. Even into the school-age years, the frequency of lower respiratory tract involvement with RSV infection remains appreciable (Fig. 5).

Reinfections in adults, although infrequently recognized, are common and are often moderately severe, especially in the elderly.[7,59-61] Among senior day-care attendees, RSV accounted for 21 percent and parainfluenza virus for 2.7 percent of identified agents causing acute respiratory infections.[7] Among patients in hospitals and long-term care facilities, RSV infection has resulted in exacerbations of chronic lung disease in 5 to 50 percent of cases and a mortality rate reaching 20 percent.[62-64]

The importance of RSV infection as a cause of hospitalization in previously healthy adults has been recognized more recently. Of 1195 adults admitted to a hospital with community-acquired pneumonia in Ohio, 4.4 percent had RSV infection. RSV was one of the four most common pathogens identified, and among viral agents it was second only to the combined influenza viruses, which were identified in 5.4 percent of patients.[8] Diagnosis was made only by serologic tests, and therefore the true rate of infection may have been greater.

These infections are poorly characterized in normal adults, because they are infrequently diagnosed and are clinically similar to many other viral infections, including influenza (Fig. 6). However, upper respiratory tract infections caused by RSV tend to last longer than those caused by other common respiratory agents, are more likely to be accompanied by a prolonged productive or "bronchitic" cough, and are more likely to be complicated by wheezing.[7,19,60] Findings on chest roentgenograms frequently suggest the presence of bacterial infection (Fig. 7). Forty percent of patients in one study in Ohio had roentgenographic evidence of pneumonia or consolidation, and in 35 percent of these patients the distribution was lobar. Furthermore, the clinical manifestations of RSV infection may mim-

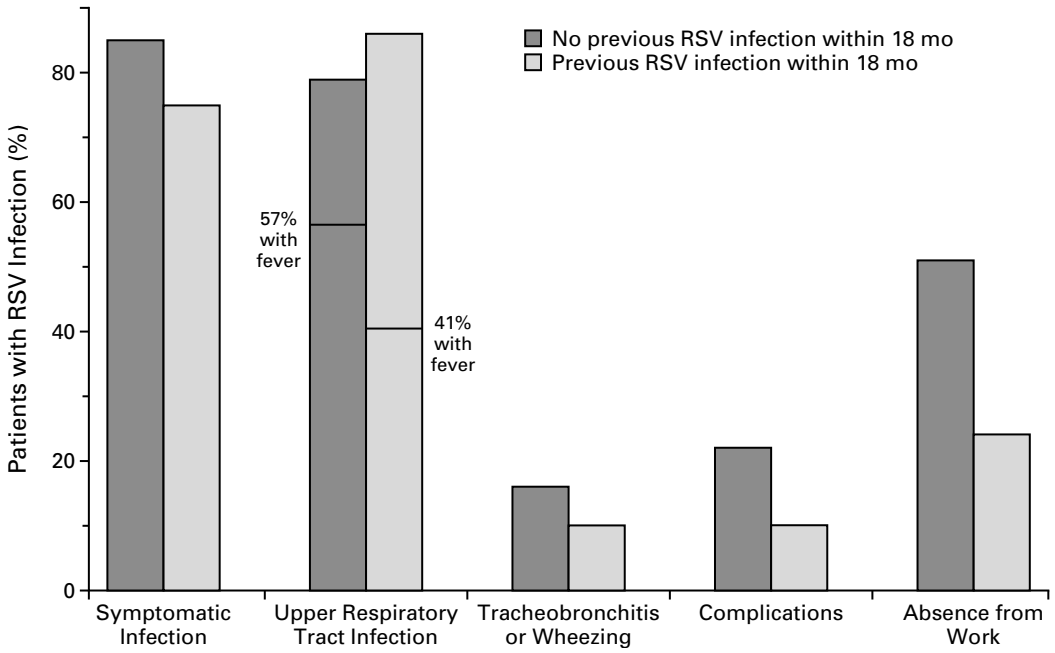

Figure 6. Clinical Manifestations and Effects of Acute Respiratory Syncytial Virus (RSV) Infection in 74 Adults, According to the Presence or Absence of RSV Infection within the Previous 18 Months.

The adults ranged in age from 20 to 62 years. Data are from Hall and McCarthy.[24]

ic those of decompensated underlying cardiopulmonary disease rather than acute viral infection.[65]

IMMUNITY

The high frequency of recurrent infections is indicative of the puzzling immune response to RSV and parainfluenza viruses and the difficulty of developing an effective vaccine. Naturally acquired immunity is neither complete nor durable. Nevertheless, protection against severe disease develops after primary infection. The components of the response providing this partial immunity are incompletely defined. Much of our current knowledge derives from the unfortunate first vaccine trials in the 1960s, which used a formalin-inactivated vaccine.[66-69] Immunized children had more severe disease than controls when they were subsequently naturally infected with RSV; 80 percent required hospitalization, as compared with 5 percent of controls. RSV was isolated from the lower respiratory tract of two children who died, and their lungs contained eosinophilic infiltrates.[69] The concurrently evaluated vaccine made from inactivated parainfluenza virus produced no augmentation of disease.

Several abnormalities of the immune response to inactivated vaccine, as compared with the response to natural infection, were subsequently detected, which suggested that protection against RSV requires a balance between humoral and cellular immunity. Vaccinated persons lacked specific mucosal antibodies, and their serum antibodies had deficient neutralizing and fusion-inhibiting activity, suggesting that formalin inactivation selectively modified epitopes within the important surface glycoproteins G and F.[70] In addition, peripheral eosinophilia and enhanced lymphocytic proliferative responses to RSV developed in some vaccinated persons.[11,71]

The relative roles of the humoral and cellular components contributing to RSV immunity in both protection and pathogenesis have been debated. In general, secretory and serum antibodies primarily protect against upper and lower respiratory tract infections, respectively, whereas cellular responses function more in controlling and terminating infection.[72,73]

Although serum antibody levels are not closely predictive of the risk of infection or illness, specific antibodies, particularly those against the F and G proteins and those of the IgG1 subclass, have some protective effect.[73,74] In rats, the administration of monoclonal antibodies against F and G proteins provides nearly complete protection of the lower respiratory tract, but not of the upper respiratory tract, against RSV challenge.[75] In infants, high levels of maternally derived or exogenous neutralizing antibody have a beneficial effect.[11,73,76]

Cell-mediated immune responses are probably most important in recovery and viral clearance. The fact that patients with compromised cellular immunity have severe, prolonged disease indicates the importance of CD4 and CD8 T cells in controlling infection. The exaggerated cellular response engendered by forma-

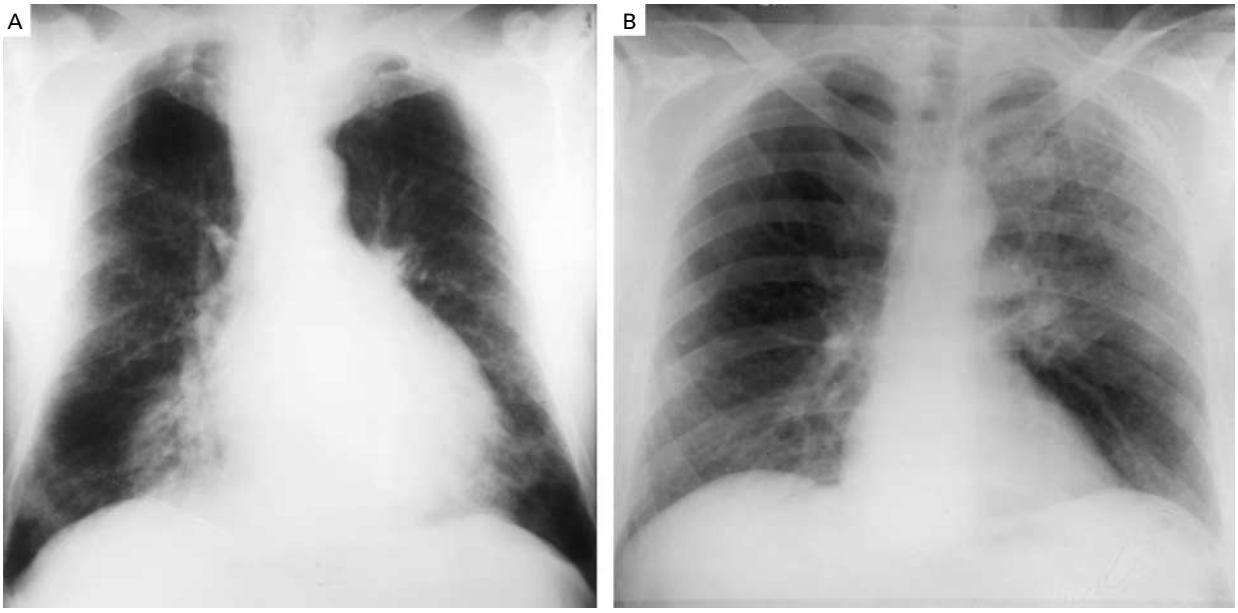

Figure 7. Roentgenographic Findings in Two Adults with Pneumonia Induced by Respiratory Syncytial Virus (RSV) Infection.

The roentgenogram in a 62-year-old man with RSV pneumonia and underlying chronic lung disease shows diffuse bilateral interstitial infiltrates (Panel A). The roentgenogram in a 55-year-old man with RSV pneumonia and chronic bronchitis shows predominantly alveolar and interstitial infiltrates in the left upper lobe (Panel B).

lin-inactivated vaccine, consisting of eosinophilia and hemorrhagic necrosis that apparently arise from the response of types 1 and 2 helper T cells, has been reproduced in animals.[11,77]

DIAGNOSIS

Diagnostic methods include viral isolation and immunofluorescence and enzyme-linked immunosorbent assays that detect antigen. Kits for the rapid screening of children have an average sensitivity and specificity of 80 to 90 percent (range, 60 to 95 percent).[78] Detection of nucleic acid by the reverse-transcriptase polymerase chain reaction (RT-PCR) offers greater sensitivity. Currently, these are primarily research tools, but multiplex RT-PCR kits that detect several viruses simultaneously are being developed.[79]

Despite the availability of multiple tests, the ability to diagnose RSV and parainfluenza virus infections has been limited and fraught with problems. The detection of antigen in nasal specimens from elderly and immunocompromised patients is an insensitive method,[47,49,54,80] and acute infection, during which viral shedding is greatest, may have occurred before the patient seeks care. More important, clinicians' low index of suspicion for these infections in adult patients results in the infrequent use of diagnostic assays.

PROSPECTS FOR IMMUNIZATION

The lack of durable immunity and of full understanding of its complexity are obstacles to effective immunization. A vaccine must offer protection that is better than that from natural infection and must be effective in the first weeks of life.

Controlling reinfections in older and immunocompromised patients may require different vaccines and strategies from those used for infants. Prophylaxis against repeated infection has the potential advantages of greater safety, since some natural immunity already exists, and more options for vaccine development since previous immunity can be augmented in a variety of ways. Nevertheless, more durable immunity than that provided by natural infection would be required, since reinfections can occur within a few weeks.[56,59] Immunization of persons at highest risk to prevent severe disease rather than infection appears to be the most viable alternative.

After the trials of inactivated vaccine, efforts focused on developing attenuated vaccines. The first RSV vaccines, consisting of temperature-sensitive or cold-passaged mutants, were effective in adults, but in children they were too virulent, too attenuated, or unstable, with reversion to wild-type virus.[11] Strategies have subsequently been used to develop improved candidate strains and vaccines from purified surface glycoproteins, DNA, and synthetic peptides.

Candidate subunit vaccines are also being explored.[11,81] These could be useful in seropositive groups at high risk; in addition, immunization of pregnant women may offer enhanced protection of their newborns by augmenting humoral and breast-milk antibody.[82] Candidate subunit F and FG vaccines have been produced from purified viruses, recombinant vectors, and plasmids containing complementary DNA of the F and G genes.

Live attenuated vaccines have the potential advantages of intranasal administration and induction of both systemic and mucosal immunity. Candidates, derived from previous cold-processed or temperature-sensitive mutants by repetitive rounds of chemical mutagenesis, have mutations that provide better attenuation, stability, and immunogenicity.[83-85]

Reverse genetics (which involves introducing various mutations into the viral genome and then investigating the effects of the mutations) has generated new candidate strains with cold-passage and temperature-sensitive attenuating mutations at sites 248 and 404 and also with the deletion of the small hydrophobic protein of RSV. Another candidate strain adds a further missense mutation that causes attenuation. Both appear promising as vaccine candidates in seropositive subjects.[86]

Recombinant genetic engineering is a powerful tool for meticulous crafting of improvements by the construction of full-length RSV complementary DNA that produces transcripts of infectious RNA.[87,88] The viral genome can be precisely designed for optimal immunogenicity and attenuation, while detrimental effects are eliminated.

Attenuated parainfluenza virus vaccines have been developed from both human and bovine strains. Bovine parainfluenza virus type 3 is closely related antigenically to human parainfluenza virus type 3, protects against challenge with human parainfluenza virus type 3, and replicates poorly in humans.[89] One bovine type 3 vaccine was immunogenic in seronegative but not in seropositive children.[90] However, a human cold-adapted type 3 vaccine appears promising in both seropositive and seronegative children as young as six months. Reverse genetics has produced an attenuated chimeric parainfluenza virus type 1 that contains type 3 internal proteins with the type 1 surface glycoproteins F and hemagglutinin neuraminidase.[91]

PROPHYLAXIS WITH IMMUNE GLOBULIN

One approach to prophylaxis in populations at high risk is augmentation of neutralizing antibody to the F and G proteins by external administration and maternal immunization.[54,76] Prophylactic administration of immune globulin containing high titers of RSV neutralizing antibody or monoclonal antibody against F protein has prevented lower respiratory tract infection in animals.[75] In humans the primary effect is to diminish the severity of illness.[11,76] Monthly administration of RSV hyperimmune globulin or monoclonal antibody against F protein (palivizumab) in premature infants or infants with chronic lung disease signif-

icantly reduced the risk of subsequent hospitalization for RSV infection.[76] However, in infants with cyanotic cardiac disease, the use of prophylaxis was associated with an increased risk of adverse outcomes. On the basis of these studies, the American Academy of Pediatrics recommends prophylaxis during the RSV season for high-risk infants without cyanotic heart disease.[76]

THERAPY

Currently the only therapy for RSV infection is aerosolized ribavirin, a synthetic guanosine analogue and broad-spectrum antiviral agent that is approved only for hospitalized infants. Administration of ribavirin has been associated with improved oxygenation, improved clinical scores, and diminished levels of secretory mediators of inflammation associated with severe wheezing and disease.[11,45] However, the use of ribavirin has been limited because it is expensive and because a beneficial effect on clinical outcome remains unproved.[76]

Ribavirin has also been tried therapeutically and prophylactically for RSV and parainfluenza virus infections in immunocompromised patients. Prospective trials are under way to evaluate its use as preemptive therapy for preventing disease in bone marrow transplant recipients.[92]

Intravenous and inhaled human immunoglobulin, RSV hyperimmune globulin, and monoclonal antibody have been used to treat limited numbers of patients with RSV infection.[93-95] The therapeutic benefit has generally been marginal. However, uncontrolled studies of immunocompromised patients suggest that RSV hyperimmune globulin or monoclonal antibody may have some therapeutic and prophylactic benefit, which may be greater when either agent is combined with ribavirin.[47,48,54,96]

Novel antiviral agents may be added to the armamentarium. Reverse genetics has created a recombinant RSV that expresses potentially therapeutic levels of interferon-γ and appears to protect mice against reinfection without inhibiting the immune response to vaccine.[97] The search for domains of the genome with specific functions has produced synthetic peptides of active regions of RSV and parainfluenza virus type 3 fusion proteins that are being examined for their antiviral activity.[98,99]

CONCLUSIONS

RSV and the parainfluenza viruses have long been acknowledged as the primary respiratory pathogens among young children. More recent is the recognition that these viruses cause a considerable disease burden throughout life. The consequences of repeated infections are most marked in elderly and immunocompromised persons. Even in otherwise healthy persons, reinfections often require medical attention, but they are generally undiagnosed and unrecognized. However, these reinfections may spread from healthy persons to those at high risk. Control may require the use of novel vaccines and immunoprophylaxis in strategies as diverse as the populations infected.

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