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Respiratory Syncytial Virus

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Respiratory syncytial virus (RSV) was first isolated in 1955 from a chimpanzee, and its infectivity in humans was documented the next year. It was named respiratory syncytial virus because of its characteristic ability to induce syncytia (i.e., multinucleate mass of protoplasm produced by the merging of cells) in tissue culture cells. It was soon recognized that RSV is a very common etiologic agent of childhood respiratory infections throughout the world. It has been estimated that in the United States every year 100,000 children are hospitalized and 2,000 young children die due to RSV infection.

Several features of RSV are characteristic. RSV is the most common causative agent of bronchiolitis and pneumonia, typically in very young children. The regular yearly epidemics are familiar to all clinicians. Immune mechanisms seem to play a key role in the development of severe RSV infection, but our understanding of the pathogenesis is still incomplete. The molecular structure of RSV is now well described, permitting studies with different viral proteins. There are two distinct groups of RSV and probably several subgroups. Molecular epidemiologic studies now in progress may answer the question of why repeated infections occur throughout life in spite of pre-existing RSV antibodies.

RSV can be detected from nasopharyngeal mucus by commercial tests within an hour, and specific antiviral chemotherapy with ribavirin is available. Recent studies suggest that β-adrenergic drugs may be beneficial in some patients with bronchiolitis. Several different approaches to develop a safe and effective vaccine are now in progress.[1–8]

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Agent

RSV is a pleomorphic, enveloped, cytoplasmic virus containing single-stranded, negative-sense RNA. The RNA is associated with viral proteins, consisting of a nucleocapsid core that is packaged within a lipid envelope. RSV is classified in the genus Pneumovirus, which belongs to the family Paramyxoviridae. The Paramyxoviridae family also includes two other genera, Paramyxovirus (containing, e.g., parainfluenza virus types 1, 2, and 3 and mumps virus) and Morbillivirus. The genera are differentiated by the diameter of the helix, the number of genes, and the nature of their surface glycoproteins.[9] The diameter of the RSV helix is 12 to 15 nm. The surface G glycoprotein of the virus lacks neuroaminidase and hemagglutinin. The RSV genome contains 15,222 nucleotides. Complementary DNA (cDNA) cloning has identified ten different viral genes, each coding for a single protein. The sequences of each gene have been described.[10] The characteristics of these genes differentiate RSV from the other members of Paramyxoviridae.

Eight of the ten RSV proteins are present in infected cells and in the virions, and therefore are structural proteins (Table 1). The disulfide-bonded glycoprotein (F, fusion protein) and the large glycoprotein (G, attachment protein) are surface proteins and are the major antigenic determinants of the virus. They are the RSV proteins inducing neutralizing

TABLE 1
Proteins of Respiratory Syncytial Virus Strain A2*

Protein	No. of Amino Acids	Location	Function
G	298	Envelope	Attachment to host receptor
F	574	Envelope	Viral penetration Syncytium formation
M	256	Envelope	Inner lining of viral envelope
22Kd (M2)	194	Envelope	Inner lining of viral envelope
N	391	Nucleocapsid	Structural protein
P	241	Nucleocapsid	Component of polymerase complex?
L	2,165	Nucleocapsid	Polymerase of nucleocapsid?
SH (1A)	64	Surface of infected cells	Not known
NS1 (1C)	139	Not in virion	Not known
NS2 (1B)	124	Not in virion	Not known

*Modified from Chanock et al: Respiratory syncytial virus, in Evans AS (ed): *Viral Infections of Humans. Epidemiology and Control,* ed 3. New York, Plenum Medical Book Company, 1989, pp 525–544; and from Collins PL: The molecular biology of human respiratory syncytial virus (RSV) of the genus pneumovirus, in Kingsbury DW (ed): *The Paramyxoviruses.* New York, Plenum Press, 1991, pp 103–162.

and protective antibodies. The G protein mediates viral attachment. The F protein mediates viral penetration and syncytium formation. In addition, the small hydrophobic protein (SH), the matrix protein (M), and the M2 protein are envelope-associated proteins. The nucleoprotein (N), the phosphoprotein (P), and the large nucleoprotein (L) are present in the RSV nucleocapsid. NS1 and NS2 are nonstructural proteins; that is, they are found only in infected cells but not in virions.[7, 11]

RSV was long considered to display minimal antigenic heterogeneity. However, two major groups of RSV, A and B, with antigenic differences on the G, F, N, and P proteins, have now been identified.[12, 13] The viral groups can be identified with monoclonal antibodies against the major structural proteins,[12, 13] by P-protein mobility analysis,[14] by the nucleic acid hybridization technique,[15] or by a polymerase chain reaction–based assay.[16] The G protein is the most variable protein, with only 53% homology in the amino acid sequences between the proteins of the A and B groups. In contrast, the F and N proteins have a high degree of genetic and antigenic homology between the two groups. Both F and G proteins have several distinct antigenic sites.

Most recent data have shown considerable genetic diversity among groups A and B. The G-protein sequences may differ 20% in different group A lineages[17] and 9% in different group B lineages.[18] These are proposed to be called subgroups and are designated by numerals.[19] Six subgroups within group A and three within group B have been described by Anderson and colleagues.[20]

The steps in the replication of RSV are schematically shown in Figure 1. The virus attaches the cell through G protein. The receptor is not known. The viral envelope fuses with plasma membrane of the host cell through F protein. After penetration, the nucleocapsid of the virus is released into the cellular cytoplasm, where the replication takes place. The viral RNA serves as a template for messenger RNA. The messenger RNA serves as a template for translation of viral proteins and complementary RNA serves as a template for transcription of virion RNA.[3] The viral antigens can be demonstrated in 9 hours in cell culture and infectious virus, in 11 to 13 hours. Human RSV replicates in several animal species, including mice, rats, guinea pigs, ferrets, and chimpanzees.[3, 7]

Epidemiology

Age

RSV is the only virus that preferentially induces severe respiratory infection during the first months of life. Primary RSV infection occurs most often between the age of 6 weeks and 2 years. The peak incidence of RSV bronchiolitis and pneumonia is between the ages of 2 and 6 months. RSV infection is rare in children less than 1 month old.[21, 22] Recently, however, Avendano and colleagues[23] from Chile reported on 239 patients with RSV infection, 28% of whom were less than 1 month old. In Rochester, New York, 70% of the hospitalized RSV patients were under 6 months old.[6] In Australia, 90% of RSV

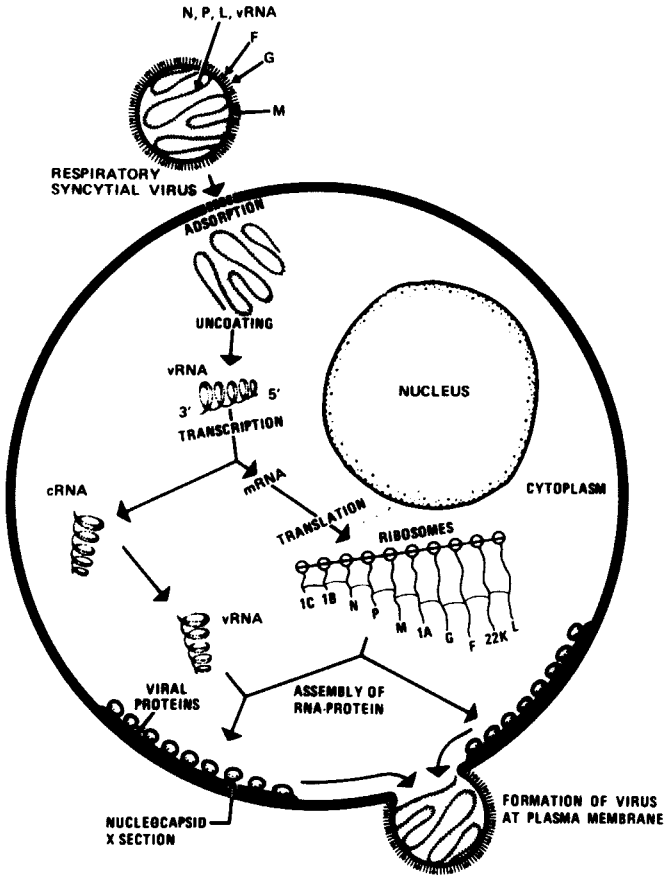

FIGURE 1
Schematic representation of the replication of respiratory syncytial virus. The letters indicate different viral proteins. *vRNA* = viral RNA; *mRNA* = messenger RNA; *cRNA* = complementary RNA. (From Anderson LJ: Paramyxoviridae: Respiratory syncytial virus, in Lennette EH, Halonen PH, Murphy FA (eds): *Laboratory Diagnosis of Infectious Diseases. Principles and Practice,* vol II. New York, Springer-Verlag, 1988, pp 540–570. Used by permission.)

detections were in children less than 1 year old.[24] By 3 to 4 years old, all children have been infected.[25–27] During recent years, it has become evident that adults and especially elderly people have symptomatic RSV infections more often than reported earlier. Complement-fixing antibody for RSV has been documented in different studies in 33% to 99% of adults.[5] Several epidemics in nursing-home patients and institutionalized young adults have also been reported.[28]

Incidence and Prevalence

Serologic studies in the 1960s showed that about half of the infants are infected during their first RSV epidemic and almost all children, after their second RSV epidemic. A family study in Houston showed the infection rate to be 69% during the first year of life and 83% during the second year of life. Risk of re-infection was 33% during year 4.[25] In a day-care center study the rate of infectivity was even higher. Of the seronegative children, 98% were infected during their first epidemic and 74% and 65% during their second and third epidemics, respectively.[29] In a recent study from Sweden, 87% of children had RSV antibodies at the age of 18 months.[26]

In about 40% of patients with primary RSV infection, a lower respiratory tract infection may develop.[30] In a prospective study of 1,179 infants in Tucson, the incidence rate for lower respiratory tract infection was 12 per 100 children in the first year of life.[22] In Chapel Hill, bronchiolitis has been estimated to occur in 6% to 7% of children per year.[31] There is less information from developing countries, but RSV also plays a major role there.[27, 32] Most incidence and prevalence figures are likely to be too low, since no study has included a combination of sensitive antigen detection assays, virus isolation, and sensitive IgG serology, which have all been shown to be necessary to obtain optimal detection of the RSV infection.[33–35] In addition, many epidemiologic studies were carried out more than 20 years ago, when the viral detection techniques were less sensitive. For example, the conventional complement-fixation serologic test may detect only half of the RSV cases detected by enzyme-linked immunosorbent assay (ELISA).[3, 4]

RSV is the most common etiologic agent to induce respiratory tract infection necessitating hospitalization. In studies in Turku and Wien, 49% and 55% of the hospitalized children with verified respiratory virus infection, respectively, had RSV infection.[36, 37] One of 100 primary infections leads to hospital admission.[22, 38] It has been estimated that almost 100,000 children in the United States experience yearly RSV infection requiring hospitalization.[25]

Seasonal Occurrence

RSV infection has a clear-cut epidemic nature throughout the world. In temperate climates it usually occurs yearly during the fall and winter. It usually begins in the late fall and peaks in November to March.[39] The epidemic lasts 5 to 6 months and peaks during the third or fourth month (Fig 2). Thus the actual month of peak infection varies a little from year to year. The intervals between peaks may be short or long. The spread of the epidemic is slower and the duration is shorter than that of influenza A, which also induces winter epidemics. Only very rarely is RSV found during the summer.

This pattern of RSV infection has been consistent in most countries over the last 20 to 30 years and variations are rare. In Finland, RSV has ap-

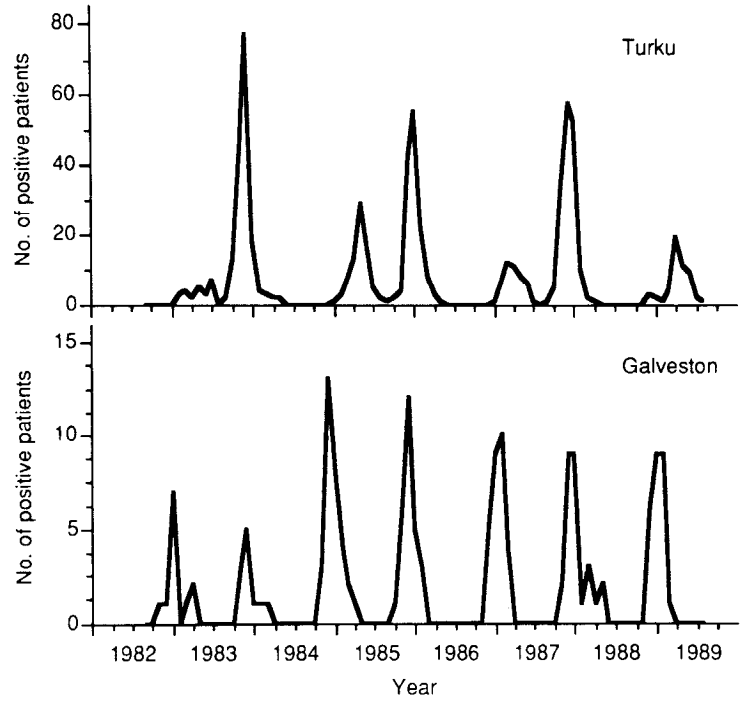

FIGURE 2
Numbers of hospitalized patients by month with respiratory syncytial virus infection in Turku, Finland, and Galveston, Texas, during 1982 to 1989.

peared during the 1980s in double-humped outbreaks, with a small outbreak occurring during the late spring and a second major outbreak during the following autumn (see Fig 2).[40] Hence, the major RSV epidemics in Finland have occurred in 2-year cycles. In Australia, RSV epidemics occur each year, with a peak in June to August with some variation.[24] In tropical countries, RSV outbreaks coincide with the rainy season.[41] The occurrence of RSV epidemics is inversely related to temperature and to the number of hours of sunshine.[42]

There are now many epidemiologic studies of group A and B RSV infections in the United States and other countries. Monto and Ohmit[43] showed that the two RSV groups existed in one community since at least 1965. In almost all epidemics, groups A and B have been found. The occurrence of outbreaks with predominantly group A RSV or predominantly group B RSV has varied according to the year and country studied.[44] Many studies have shown that different groups can predominate in different geographic locations during the same year. A study from 14 laboratories in the United States and Canada found 63% of 483 RSV isolates to be within group A and 24% within group B.[20] Furthermore, six subgroups within group A and three within group B were demonstrated. Six subgroups of group A were isolated during the same RSV season in the same laboratory. The predominance of group A RSV infections may be explained by the findings that group A virus induces greater protection from subsequent group B infection than the converse.[45]

Storch and colleagues[19, 46] showed that widespread genetic variation of the G-protein gene occurs between group A strains obtained from a single epidemic. However, strains obtained from the same family were identical. In agreement, Cane and colleagues[47, 48] showed by nucleic acid sequencing that multiple lineages of group A RSV co-circulate in a single epidemic and in different parts of the world. On the other hand, viruses isolated from different parts of the world at similar times may also be virtually identical.

Transmission

RSV infections are transmitted by large droplets, through fomite contamination, or by direct contamination with infected secretions. Close contact appears to be necessary for infection to spread from one person to another. In one study, no one sitting at a distance of greater than 1.8 m from RSV-infected infants became infected.[49] The most important route of transmission appears to be self-inoculation with fingers contaminated with infected secretions. The virus can persist in a viable form on cloth gowns and paper tissue for 45 minutes, and on countertops for

up to 6 hours.[49] The fingers transmit the virus to the nasal mucosa or conjunctivae, from where the virus spreads to the upper respiratory tract. The incubation period is usually 2 to 8 days (median, 5 days).[6] The infection spreads to the lower respiratory tract within a few days of the onset of symptoms. The mechanisms of spreading are not well understood. Viremia has not been described in normal subjects, but viral antigens have been found in circulating blood mononuclear cells. RSV is secreted in nasopharyngeal secretions usually for 5 to 10 days.[50, 51] In a recent study,[35] 40% to 60% of the patients stopped shedding RSV 8 to 10 days after the onset of illness (Fig 3). Some infants can shed RSV for up to 3 or 4 weeks or longer. Longer periods of virus shedding have been noted in immunosuppressed children, and shorter durations in older children and adults.[50] RSV infection spreads actively in closed environments. In a family study, RSV infected 46% of the family members.[50]

Risk Factors

Several risk factors for RSV lower respiratory tract infection have been described. In the early months of life, the infection is more common in males. Furthermore, RSV infection is more common in children born during the summer months approximately 6 months before the outbreak, in those sharing a bedroom with other children (especially when there are two or more sharing the room), in day-care settings, and in infants of mothers with lower educational levels.[21, 22, 52–54] Importantly, breast-feeding for longer than 1 month has a protective role, especially for those infants of mothers with lower socioeconomic status. Infants with a low titer of RSV antibody in cord serum and minimal breast-feeding are especially at risk for RSV infection of the lower respiratory tract.[22]

The role of atopic predisposition to severe RSV infection is controversial; some studies demonstrated significantly higher risk in children with atopy compared to control children,[55, 56] while other studies showed no significant associations with atopy.[53, 57] A recent study showed that diminished lung function is a predisposing factor for lower respiratory tract infection associated with wheezing.[58] This finding would explain why decreased pulmonary function has been recorded after RSV bronchiolitis. Many studies have shown that maternal smoking increases the risk of all respiratory virus infections.[52, 59–61] McConnochie and Roghmann[60] showed that maternal smoking was associated with an increase in frequency of wheezing from 36% to 60%. Thus, prolonging breast-feeding for longer than 1 month and cessation of parental smoking should be encouraged to reduce the risk of lower respiratory tract infection in infants and children.

Pathogenesis

Despite the large number of studies on the pathogenesis of RSV infection in humans and experimental animals, the current information is fragmentary

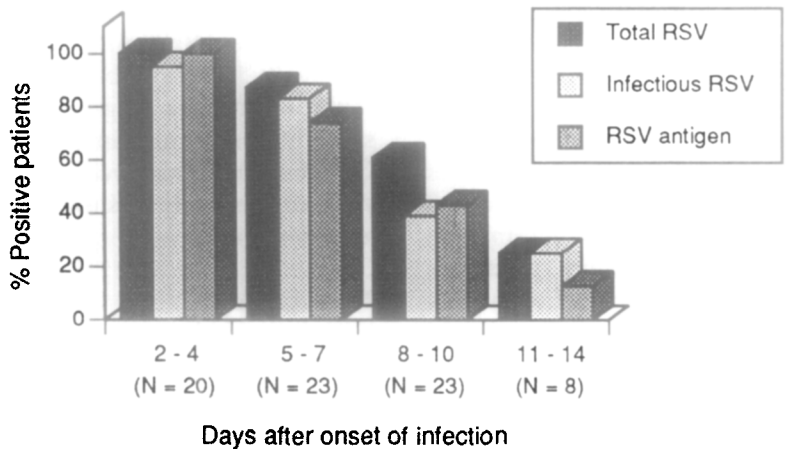

FIGURE 3
Shedding of respiratory syncytial virus (RSV) in hospitalized children. Infectious RSV was demonstrated using immunoperoxidase staining and/or by observation of the specific cytopathic effect in infected cultures. RSV antigen was detected by direct time-resolved fluoroimmunoassay. Total RSV reflects both infectious RSV and RSV antigen. (Modified from Waris M, et al: *J Med Virol* 1992; 38:111–116. Used by permission. Copyright © 1992 Wiley-Liss. Reprinted by permission of Wiley-Liss, a division of John Wiley and Sons, Inc.).

and the mechanisms of the disease are not well understood.[62-67] Studies in humans have been difficult to undertake because the infection occurs most frequently in young infants with extremely low mortality. In vitro studies with human peripheral blood mononuclear cells as well as those with nasopharyngeal specimens have produced numerous observations, but only limited data are available on the immune response in the lower respiratory tract. Several animal models have been developed, but in most species the infection is asymptomatic. Nevertheless, many clinical findings and sophisticated animal experiments suggest a key role of immune response to RSV in the pathogenesis of the infection. There appears to be a delicate balance between immunopathology and immunoprotection. A precise understanding of the mechanisms of protection against infection, development of disease, and recovery from illness is needed for development of improved therapies and an effective and safe vaccine.

Antibody-Mediated Immunity

RSV infection induces incomplete immunity to disease, even after multiple infections. The primary infection, which often involves the lower respiratory tract as bronchiolitis or pneumonia, occurs most commonly in infants at 6 weeks to 6 months, when transplacentally derived maternal IgG antibodies still exist in the circulation. These universal observations suggest that serum IgG antibodies to RSV may not be protective. One hypothesis is that maternal antibodies react with the virus in the lung, inducing immune complex–mediated pulmonary injury. However, this hypothesis has been challenged by observations that RSV bronchiolitis occurs in infants without detectable RSV antibodies. Furthermore, bronchiolitis is rare in neonates less than 6 weeks old, who have the highest serum concentrations of maternally derived antibodies. New laboratory studies, however, have shown that antibodies to F and G surface glycoproteins can enhance the in vitro infection of human macrophages. This phenomenon may in part explain the disease process in bronchiolitis.[68, 69] In in vitro experiments, RSV plus anti-RSV antibody complexes may stimulate macrophages to produce leukotriene C_4 (LTC_4), which induces bronchospasm.[70]

The failure of transplacentally acquired RSV antibodies to protect against natural infection is not fully understood. It has been suggested that either maternal IgG may not contain enough IgG3 subclass antibodies, the antibodies against appropriate RSV group or subgroups may be insufficient, or the circulating IgG antibodies may not transudate to the mucosa of the lower respiratory tract.[71] Recent studies have shown sequence diversity among the G proteins within groups A and B RSVs. If the immune response is also subgroup specific, infection by one subgroup could occur despite the presence of neutralizing antibodies specific to another subgroup.[18, 19]

Another finding that has confused understanding of the pathogenesis of RSV infection is that the children vaccinated in the early 1960s with a formalin-inactivated RSV candidate vaccine were not protected against the RSV infection, and paradoxically developed a more severe illness when exposed to natural infection. Such vaccination induced high concentrations of neutralizing and complement-fixing antibodies, and these may have reacted with the natural virus to induce harmful effects. Later, however, serum samples of the vaccinated children were reanalyzed and found to contain a large proportion of antibodies directed against nonprotective viral epitopes. These results suggest that formalin treatment altered the antigenic determinants of RSV, resulting in an aberrant host immune response. The large number of nonprotective antibodies in the serum could have formed complexes with viral antigens and induced pulmonary disease.[72]

There is, however, good epidemiologic evidence to suggest that high titers of maternal RSV antibodies can be protective against severe RSV-associated respiratory illness.[21, 22] Lamprecht and colleagues[73] found that maternal neutralizing antibody did not prevent infection but the severity of pneumonia was inversely related to the level of neutralizing antibody. High neutralizing, F and G antibody levels have also been found to correlate significantly with protection, but the protection is not complete.[74] Recent studies on mice depleted of B cells showed that mice without antibody demonstrate enhanced histopathology in the lung and have more severe RSV infection than mice with intact B-cell function. These results support the view that antibody has an illness-sparing function in RSV infection.[75] However, antibody was not needed for termination of RSV replication after primary infection. Connors and coworkers[76] found that F and G protein–induced antibodies are sufficient to mediate the resistance to RSV in the absence of $CD4^+$ T cells, $CD8^+$ T cells, and interferon-γ. On the other hand, the resistance induced by the M2 protein was mediated by $CD8^+$ T cells and to some extent $CD4^+$ T cells and interferon-γ.

Further evidence of the possible protective effects of serum antibodies has come from trials of therapeutically administered, RSV-specific IgG in infants with RSV disease. Treated patients had enhanced clearance of the virus from the upper respiratory tract and improved clinical response, compared to placebo-treated control subjects.[77-79] These

observations agree with the results of animal studies showing that lung infection by RSV can be prevented by administration of high titers of neutralizing antibodies.

RSV-specific secretory IgA appears in the nasopharynx as early as the first 3 days after the onset of symptoms of infection and often peaks between 8 and 13 days.[80] McIntosh and colleagues[81] found that the appearance of RSV-specific secretory IgA in the nasopharynx coincided with the termination of RSV shedding, suggesting that secretory IgA may play a role in the termination of infection. Similar findings were recently obtained by Waris and coworkers.[35] Specific nasal RSV antibody titers are not, however, found to correlate significantly with protection, although subjects with detectable nasal IgA antibody tended to become infected less often after challenge. Interestingly, one patient with secretory IgA deficiency resisted the challenge with RSV.[74]

Studies performed in children with RSV bronchiolitis, or pneumonia with and without wheezing or subclinical infections, have shown that most virus-infected subjects develop RSV-specific IgE antibodies.[82, 83] However, only patients with wheezing manifest prolonged, cell-bound, virus-specific IgE response and free RSV-specific IgE in their nasopharyngeal secretions. Furthermore, the occurrence of RSV-specific IgE has been associated with subsequent episodes of virus-induced wheezing.[84] In addition, the development of RSV-specific IgE correlated with increased concentrations of histamine in nasopharyngeal secretions of patients with bronchiolitis.[82] The development of virus-specific IgE response may be constitutionally determined in patients with virus-associated bronchospasm. Caswell and associates[85] reported more histamine release in response to RSV in those with bronchiolitis than in control subjects. This release would reflect latent sensitization to RSV antigens during bronchiolitis. The mechanism effecting histamine release could involve RSV-specific, IgE-inducing mast cells, basophils, and eosinophils. Increased plasma levels of histamine and a stable prostaglandin (PG) metabolite in bronchiolitis were also reported by Skoner and colleagues.[86] They found a direct correlation between plasma levels and disease severity. In general, the children who had had bronchiolitis had higher levels of histamine and prostaglandin metabolite than normal children, even when asymptomatic. Chonmaitree and colleagues[87] demonstrated that RSV can induce blood mononuclear cells to produce histamine-releasing factor in vitro. The development of RSV-specific IgE antibodies and increased histamine levels in both serum and secretions have also been demonstrated in calves infected with bovine RSV. This animal RSV infection model has many striking similarities in pulmonary pathology to human RSV infection.[88]

Cell-Mediated Immunity

Clinical and experimental studies suggest an important role for cell-mediated immunity in RSV infection. Severe and prolonged RSV infection has been observed in immunodeficiency states.[89] Different T-cell subtypes, degrees of lymphocyte proliferation, and cytotoxic T-cell responses have been reported during and after RSV infection. Welliver and coworkers [90] found fewer suppressor T cells in patients with bronchiolitis during convalescence than in patients with other forms of illness due to RSV. These observations suggest that virus-induced or immunoregulatory defects may induce increased IgE production in patients with bronchiolitis. On the other hand, Domurat and colleagues[91] found that in vitro RSV infection resulted in an increase in the number of suppressor T cells and a decrease in helper T cells.

RSV-induced lymphocyte proliferation, an in vitro correlate of cell-mediated immunity, has been observed to be high in RSV bronchiolitis and in other RSV-infected infants with bronchospasm,[92] but contrary results have also been reported.[93] The major target structure for T-cell proliferation is the F protein of RSV, and lymphocytes responding to its antigenic sites have the characteristics of helper T cells.[94] Clinical follow-up studies have suggested that alterations in RSV-specific lymphoproliferative activity may result in an increased tendency toward airway reactivity during subsequent re-infection with RSV.[92] In vitro infection of mononuclear leukocytes with RSV has been shown to decrease the response of the cells to mitogens.[95] Both $CD4^+$ and $CD8^+$ T lymphocytes have been shown to be involved in terminating RSV infection in a mouse model. Both of these cell types also contributed to the illness, suggesting that host immune response is the primary determinant of the disease.[96]

The peripheral blood lymphocytes of infants with acute RSV infection may exhibit cellular cytotoxic response against RSV-infected cells.[97] The response appears to depend on age, and increases in infants over 6 months old.[98] The development of cellular cytotoxic responses may play a role in the mechanisms of protection or immunologic injury that accompany RSV infection in humans. Studies in mice have demonstrated that passive transfer of RSV-specific cytotoxic T cells can clear RSV from the lungs, but also intensify clinical symptoms, enhance pulmonary pathology, and increase death rate.[99] Recently, Munoz and colleagues[100] demonstrated cyto-

toxic cell lines capable of protecting lungs from RSV infection without producing an increase in morbidity and mortality. These observations strongly suggest that major histocompatibility complex (MHC) class I–restricted cytotoxic T cells have an important role in clearing RSV from the lungs.

A series of studies using recombinant vaccinia viruses expressing different RSV proteins have shown in mice that the RSV-specific cytolytic T-cell response is specific for viral protein. The major target is a membrane-associated 22Kd protein followed by intermediate recognition of F or N proteins.[101, 102] Interestingly, the 22Kd RSV protein does not induce detectable RSV-specific antibodies in mice.[103]

Inflammatory Mediators and Cytokines

There is increasing evidence that RSV infection can result in the release of mediators and cytokines from target cells. Early studies clarified the role of interferon in RSV infection. RSV was found to be a poor inducer of interferon-α in vitro and in vivo, in contrast to other viruses such as influenza A virus.[104, 105] The concentrations of interferon-α in nasopharyngeal secretions do not correlate with the severity of illness.[106] In vitro production of interferon-α is reduced during RSV bronchiolitis, and returns to normal after illness.[107]

RSV antibody complexes can activate the arachidonic acid pathways of human neutrophils in vitro.[108] Most RSV-infected patients have high levels of LTC_4 in the respiratory tract during the acute phase of infection. LTC_4 is an arachidonic acid metabolite that can cause bronchoconstriction. The levels in wheezing subjects appear to be significantly higher than in nonwheezing subjects. Furthermore, LTC_4 was detected more often in patients who developed an RSV-IgE response than in patients who did not.[64] Garofalo and associates[109] found LTC_4 in 83% of patients with bronchiolitis, and LTD_4 and LTB_4 in about 30%. The mean partial arterial pressure of oxygen was lower in those with detectable LTB_4 than in those without, suggesting that LTB_4 may have an important role in the pathogenesis of bronchiolitis. LTB_4 is an effective chemoattractant for neutrophils and eosinophils. A further study by Garofalo's group[110] showed that concentrations of eosinophil cationic protein in nasopharyngeal secretions were significantly higher in RSV bronchiolitis than in RSV infections without wheezing, and the concentrations correlated with the severity of the disease. Eosinophil cationic protein is considered to have a major role in the pathogenesis of asthma and these findings lend further support to the hypothesis that asthma and virus-induced respiratory infection with expiratory wheezing are pathogenetically related.

RSV has been shown to induce interleukin-1 (IL-1) and IL-1 inhibitor production by human mononuclear leukocytes. The net effect is inhibition of IL-1 activity.[111, 112] Further studies showed suppression of intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function–associated antigen (LFA-1) by human mononuclear leukocytes compared to the degree of expression induced by influenza virus.[113] These phenomena may result in cell cycle arrest of virus-specific lymphocytes and may in part explain the recurrence of RSV infection in immune individuals.

Tumor necrosis factor (TNF)-α can be detected in serum from patients with RSV-induced lower respiratory tract infection.[114] However, the concentrations are low, possibly because RSV has only minimal effects on the production of TNF by blood mononuclear phagocytes in vitro. In contrast, RSV-induced alveolar macrophages produce significant amounts of TNF.[115] Panuska and coauthors[115] suggested that TNF produced by alveolar macrophages may play a critical role in limiting pulmonary RSV infection, because TNF has antiviral activity. These observations agree with those of Becker and colleagues[116] who demonstrated that RSV infection of human alveolar macrophages resulted in the production of TNF, IL-6, and IL-8. They suggested that through cytokine production, alveolar macrophages may have an important role in limiting RSV infection in the bronchoalveolar region of the lung.

Platelet-activating factor (PAF) is an important mediator in asthma. It has several biologic effects in various parts of the immune system. Recently, Villani and coworkers[117] demonstrated that RSV infection in a human monocytic cell line induced the synthesis of PAF.

Pathology

RSV infects respiratory epithelial cells. In addition, human blood mononuclear cells and human alveolar macrophages have been shown to be infected with RSV.[91, 118] Organ systems outside the respiratory tract do not become infected in patients with normal immune systems. However, in immunocompromised patients, RSV has been recovered from the liver, spleen, and myocardium.

There is little or no information about the pathologic changes associated with RSV in mild pneumonia and bronchiolitis. Autopsy studies have revealed lymphocytic peribronchial infiltration in bronchiolitis.[119] There was no cellular infiltration of alveolar tissue. Because RSV is attracted to respiratory epithelium, proliferation and necrosis of the epithelium develop. With the immunoperoxidase method of antigen detection on formalin-fixed, paraffin-embedded

lung tissue, RSV antigen was demonstrated in epithelial cells from throughout the lower respiratory tract.[120] Many RSV-positive cells had paranuclear eosinophilic inclusions. Edema can be found in submucosal and adventitial tissues. All these changes induce an obstruction of small airways by cellular debris, making expiration of air difficult and resulting in hyperinflation. Marked disturbances in respiratory mechanisms develop. An increase in respiratory resistance and a pronounced reduction in forced expiratory flow have been reported.[121] In pneumonia, interalveolar walls are infiltrated with mononuclear cells and are thickened. Extensive pneumonic consolidation by alveolar debris containing protein, macrophages, epithelial cells, and numerous syncytial multinucleated giant cells with eosinophilic cytoplasmic inclusions have been found.[120, 122] RSV antigen has been investigated in two children with fatal bronchiolitis. Little virus was found in the lungs. By contrast, in a child with RSV-associated pneumonia, large amounts of viral antigen were detected.[123]

Clinical Features

The clinical picture of RSV infection varies according to the age of the patient. The primary RSV infection at the age of 6 weeks to 2 years is usually symptomatic and involves the lower respiratory tract. Asymptomatic primary RSV infection in children is rare. Repeated infections in older children are usually less severe. Table 2 shows the clinical spectrum of 2,903 RSV infections in hospitalized young children in several different countries. Respiratory tract infection associated with expiratory wheezing (i.e., bronchiolitis, wheezy bronchitis, and asthma; 52%) and pneumonia (21%) were the most common clinical manifestations. RSV infections in neonates differ from those in older children; apnea may be the only symptom of infection. Acute otitis media is the most common bacterial complication. The mortality in healthy children is extremely low, but life-threatening infections are common in immunocompromised patients and in patients with cardiac abnormalities. Pneumonia is the most common manifestation in elderly people.

Upper Respiratory Tract Infection

Isolated upper respiratory tract infections associated with RSV have been noted, especially in older children and adults during re-exposure. The common symptoms are rhinorrhea, nasal congestion, pharyngitis, and cough.[50, 127, 128] RSV infection is a less febrile illness than other respiratory infections.[129, 130] RSV-induced upper respiratory tract infection cannot be clinically differentiated from upper respiratory tract infections induced by other respiratory viruses.[131] Some studies, however, suggest that common colds induced by RSV may be more prolonged and severe than those induced by other viruses.[50]

Bronchiolitis

Bronchiolitis is a clinical syndrome. It has been used as a diagnosis since 1940.[132] It is evident that the diagnostic criteria vary in different centers in the United States and in other countries.[133, 134] The major clinical feature of bronchiolitis that is accepted by all clinicians is expiratory wheezing associated with rhinorrhea and cough. McIntosh[135] suggested that the term bronchiolitis should be reserved for children under 12 months old. Studies by Mulholland and colleagues[136] included patients younger than 15 months old and those by Welliver and coworkers[137] included children younger than 22 months. Henderson and colleagues[29] defined illnesses with expiratory wheezing of all ages as bronchiolitis, and suggested that the limitation to the first few months of life should be modified. In many European countries a diagnosis of bronchiolitis is given only to severely sick infants, and all of them are treated in the hospi-

TABLE 2
Clinical Findings (%) of Respiratory Syncytial Virus Infection in 2,903 Hospitalized Patients

	Carlsen et al[124] (1983; N = 551; Norway)	De Silva and Hanlon[24] (1986; N = 768; Australia)	Galinovic et al[125] (1987; N = 207; Croatia)	Avendano et al[23] (1991; N = 239; Chile)	Mufson et al[126] (1991; N = 405; USA)	Ruuskanen[37] (1992; N = 733; Finland)
Upper respiratory tract infection	8	3	59	4	23	41
Croup	1	2	6	NS	11	3
Wheezing*	86	71	11	42	27	43
Pneumonia	22	3	11	71	39	18

*Includes bronchiolitis, wheezy bronchitis, and asthma.
NS = not studied.

tal. In the Tucson Children's Respiratory Study,[22] 123 cases of bronchiolitis were diagnosed and only 2 patients needed hospitalization. In another study of 213 infants with bronchiolitis, 123 patients with mild bronchiolitis were discharged from the emergency unit.[130] Given this variability in the definitions, it is not surprising that the incidence figures vary.

Combining the criteria of several authors, we propose to define bronchiolitis as a syndrome in infants less than 12 months old in whom a first attack of an acute illness, after a brief prodrome of upper respiratory symptoms, is characterized by wheezing, dyspnea, respiratory distress, poor feeding, tachypnea (≥50/min), and radiologic evidence of hyperaeration of the lung. Fine crepitation can usually be heard by auscultation.

Oxygen saturation measured by noninvasive pulse oximetry is the best method for an initial objective assessment and should be performed in all patients with bronchiolitis.[130, 136] Clinical findings may be poor predictors of hypoxemia.[138] In addition to hypoxemia (oxygen saturation ≤90–95%), "toxic" appearance (most patients appear well), gestational age of 34 weeks or younger, respiratory rate of 70/min or more, atelectasis on a chest roentgenogram, and age of 3 months or younger have been shown to predict more severe disease.[130, 136] In severe cases, hypercapnia, cyanosis, intercostal and subcostal retractions, and flaring of nasal alae may also develop. Wheezing may not occur in most severe cases, because of decreased air movement. It has been suggested that the respiratory rate is a good guide to reflect the status of oxygenation.[139] In contrast, in one recent study, respiratory rate on initial presentation did not predict the severity of bronchiolitis as measured by oximetry.[136]

Chest radiographs show changes in most patients: Hyperaeration, perihilar linear opacities, and bronchial wall thickening have all been described (Figs 4–6).[140] The pathognomonic finding is hyperaeration, which in the observer variation analysis was also the most reproducible feature of bronchiolitis.[141] Areas of collapse can also be seen. It has been stated that routine chest radiography brings very little to the treatment of bronchiolitis and chest radiographs should be taken only of patients who need intensive care, who have underlying heart or pulmonary disease, and whose clinical symptoms deteriorate.[142]

In the great majority of patients with RSV bronchiolitis, the symptoms and signs resolve within a few days after admission to a hospital. The duration of hospitalization is usually 2 to 7 days. Infants under 6 weeks old and those with underlying illnesses often need longer hospitalization.[143, 144]

Although RSV is the most common etiologic agent of bronchiolitis and virtually the only agent that induces epidemics, other respiratory viruses can also induce bronchiolitis. Welliver and colleagues[137] described parainfluenza type 1 and 3 virus–induced bronchiolitis, and many studies reported parainfluenza virus as the second most common inducer of bronchiolitis.[29, 41, 136] In addition, rhinoviruses, adenoviruses, coronaviruses, and influenza A virus may

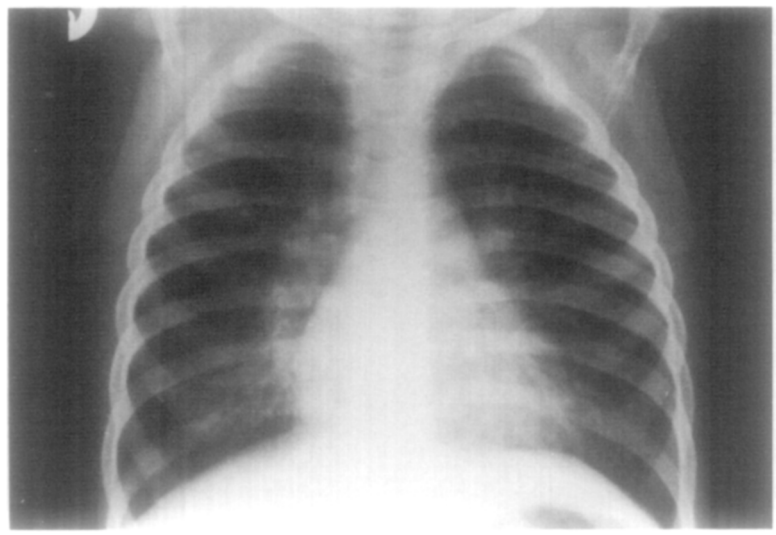

FIGURE 4
Respiratory syncytial virus bronchiolitis in a 12-month-old infant. Parahilar peribronchial infiltrates with moderate hyperexpansion can be seen. (From Wildin SR, et al: *Am J Dis Child* 1988; 142:43–46. Copyright 1988, American Medical Association.)

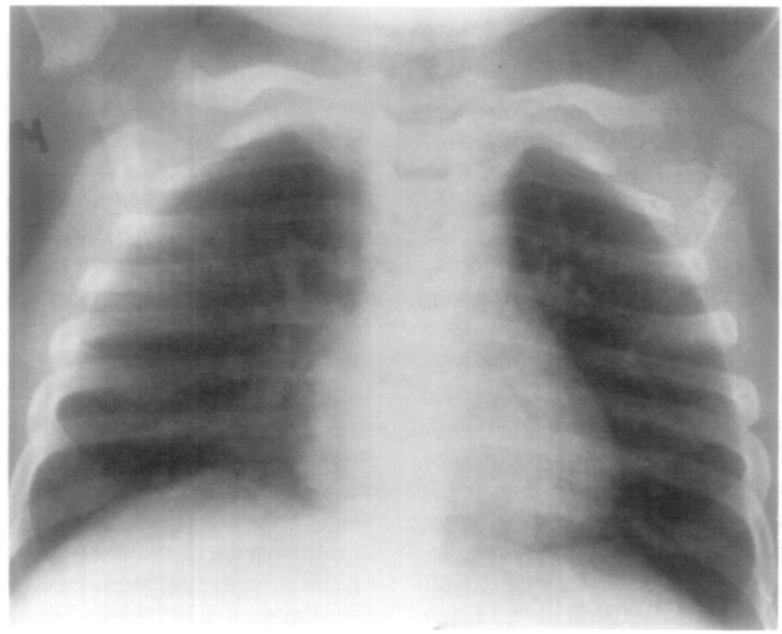

FIGURE 5
Respiratory syncytial virus pneumonia in a 14-month-old infant. Interstitial infiltrates can be seen in both lungs.

be causative agents of bronchiolitis.[29, 145] Adenovirus may induce very severe bronchiolitis with high mortality.

Numerous follow-up studies have shown that 22% to 75% of the patients with RSV bronchiolitis exhibit recurrent wheezing or pulmonary function abnormalities years later.[146] The clinical symptoms gradually decrease and disappear usually during the following 10 years.[60] In some of these patients, the symptoms continue and they can be classified as having asthma. Sly and Hibbert[147] could diagnose asthma in up to 92% of 48 patients followed prospectively for 5 years after bronchiolitis. Even after mild bronchiolitis, increased morbidity was docu-

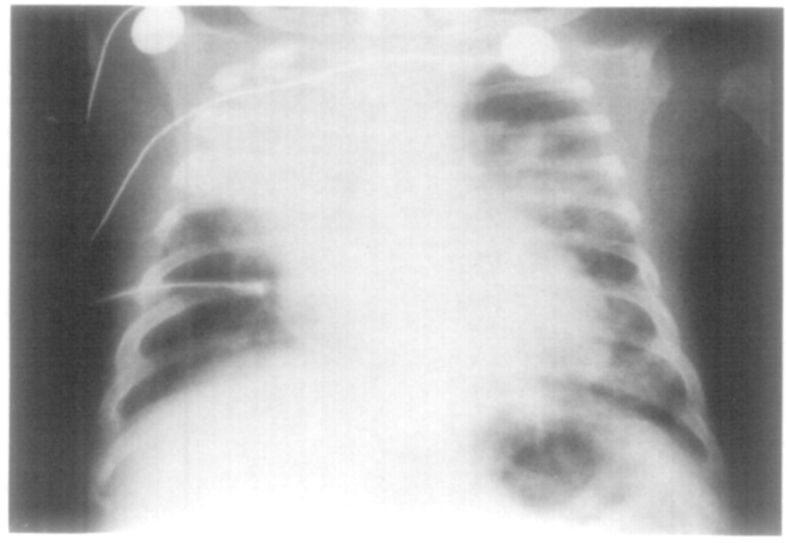

FIGURE 6
Respiratory syncytial virus and pneumococcal pneumonia in a 2-month-old infant. Consolidation of the right upper portion of the lobe and bilateral parahilar peribronchial infiltrates are seen. (From Wildin SR, et al: *Am J Dis Child* 1988; 142:43–46. Copyright 1988, American Medical Association.)

mented through the third and fourth year of life, but normal pulmonary function was found between the ages of 8 and 12 years.[60] In spite of these studies, it is not clear whether RSV can induce long-lasting or even permanent damage to the small airways and in the growing lung. It is possible that development of bronchiolitis may be restricted to subjects already genetically and anatomically at risk for pulmonary hyperreactivity. This possibility is strongly supported by the findings that pre-existing diminished lung function measured very early in life, before any respiratory illness, was found to be a risk factor for recurrent wheezing.[58] Understanding the possible long-term consequences of RSV bronchiolitis is important because inhaled corticosteroids may be an effective preventive therapy for the development of recurrent wheezy bronchitis and asthma.[148–151]

Wheezy Bronchitis

Wheezy bronchitis is an acute illness characterized by cough, rhonchi, and expiratory wheezing in young children.[152] Typically the attacks are recurrent. It has been estimated that 10% to 20% of the children wheeze in association with respiratory virus infection.[153] The most common etiologic agents that induce wheezy bronchitis are RSV, rhinovirus, coronavirus, parainfluenza viruses, adenovirus, and *Mycoplasma pneumoniae*.[145, 154, 155] It has been well demonstrated that these microbes may induce hyperreactivity of the airways.[156] In patients with repeated attacks of wheezing, Mertsola and colleagues[145] found that wheezing occurred in 58% of laboratory-confirmed viral respiratory infections.

It appears that to some extent, bronchiolitis, wheezy bronchitis, and asthma are expressions of the same pathologic process and at present there are no rigid criteria to separate these three illnesses.[156] A diagnosis of wheezy bronchitis is recommended to be used after the primary attack of expiratory wheezing (bronchiolitis) and in patients having their first attack at an age of more than 11 months.[135] The clinical picture mimics that of bronchiolitis, although usually wheezy bronchitis is less severe. Expiratory wheezing starts within 24 to 48 hours after the onset of symptoms of respiratory infection and lasts 3 to 7 days.[145] The majority of children with recurrent wheezy bronchitis stop wheezing after the age of 3 years.[155] Foucard and Sjoberg[157] found that 28% of patients still had attacks of wheezing after 12 years. These patients had more allergic manifestations than patients who stopped wheezing. In older children, wheezy bronchitis cannot be differentiated from virus-induced asthma. At present, it is evident that the use of wheezy bronchitis as a diagnosis varies considerably.[158]

Pneumonia

It is well established that RSV is the most common, single etiologic agent of childhood pneumonia. RSV infection can be demonstrated in 10% to 60% of children with pneumonia (Table 3). In hospitalized patients with RSV infection, pneumonia can be diagnosed in 20% to 40% (see Table 2). The variation is due to the different epidemiologic conditions and different diagnostic methods. If a pneumonia study is carried out during an RSV epidemic, the great majority of the cases of pneumonia will be found to be induced by RSV.[159] The diagnosis of pneumonia should be based on radiographic findings, because it is impossible to differentiate crackles of bronchiolitis and wheezy bronchitis from those found in pneumonia.[163] Furthermore, often in lobar bacterial-type pneumonia, no crackles can be heard and chest radiograph is the only way to diagnose the illness.[34] In addition to virus detection assays, the etiologic tests should include a sensitive IgG serologic assay. In two recent studies, virus culture and sensitive antigen detection assays found only 33 (69%) of 48 cases of RSV-associated pneumonia.[33, 34] It is possible that in pneumonia, the pre-existing symptoms may have lasted long enough that the virus is no longer detectable in the nasopharynx, and sensitive serology may be the only way to detect infection.

The clinical signs and symptoms of RSV pneumonia do not differentiate it from other viral pneumonias. However, usually the epidemiologic situation and the age are highly suggestive. The general condition of the children is good in most cases. Fine crackles heard from both lungs suggest the diagnosis, but they can be also heard in RSV bronchiolitis. Many patients with bronchiolitis also have pneumonia and without a chest radiograph these two illnesses are difficult to differentiate. White blood cell count, erythrocyte sedimentation rate, and serum C-reactive protein levels are within normal limits in most patients.[164]

Rice and Loda[163] saw in 97% of the chest radiographs of RSV pneumonia, diffuse interstitial infiltrates that often involved all lobes (see Fig 5). In addition, they frequently recorded hyperinflation and right-upper-lobe consolidation. Interstitial infiltrates were also recorded by Friis and colleagues.[165] In contrast, Wildin and coworkers[140] did not find interstitial infiltrates in RSV infection. Instead, they saw parahilar bronchial infiltrates in 92% and atelectasis in 41% of the patients (see Figs 4 and 6). Consolidation and alveolar infiltrates have been seen in 10% to 30% of patients,[141, 163, 166] but investigators using limited microbiologic diagnostic approaches have been unable to relate these findings to possible bacterial co-infection.[165] In general, a reliable compari-

TABLE 3
Respiratory Viruses (%) Associated With Childhood Pneumonia

	Paisley et al[159] (1984; N = 102; USA)	Turner et al[160] (1987; N = 98; USA)	Isaacs[161] (1989; N = 57; England)	Claesson et al[162] (1989; N = 336; Sweden)	Ruuskanen et al[34] (1992; N = 50; Finland)
Respiratory syncytial virus	60	28	11	20	30
Rhinovirus	6	2	9	NS	10
Parainfluenza	4	5	4	3	8
Adenovirus	1	1	7	3	10
Influenza A	1	2	0	3	2

NS = not studied.

son of different radiologic findings in RSV infection is difficult, because the descriptive terms vary widely.

Infection in Newborn

Although RSV infection is rare in the first 4 weeks of life, epidemics in neonates have been described. Hall and coauthors[127] reported RSV infection in 28% of 82 babies studied in a neonatal unit and in 35% of those hospitalized for 6 days or longer. Sixty-one percent of the babies had respiratory illness, and of these, approximately half had upper respiratory tract infection and the other half, pneumonia. Pneumonia was diagnosed more often in infants over 3 weeks old. When pneumonia during the first month of life was studied, RSV was found to make 55% of all isolates in the 40 patients studied.[167] It is important to note that in many infants, the RSV infection may be atypical; that is, the major manifestations are apnea, lethargy, irritability, and poor feeding. Interestingly, in two neonates with RSV infection who were described, fever, thrombocytopenia, and rash covering the trunk were the major clinical symptoms.[168] These observations suggest that RSV should be included in the sepsis workup of infants during RSV season.[169]

Apnea (defined as a cessation of breathing for more than 15 seconds or associated with cyanosis or bradycardia)[170] is a well-documented symptom of RSV infection. It occurs in 20% to 25% of young infants.[127, 170, 171] The mechanisms of RSV-associated apnea are not well understood. Anas and colleagues[170] found apnea to be diaphragmatic or nonobstructive; that is, a respiratory effort was absent. In a study on 58 apnea spells in two infants, two types of apnea were found.[172] Nonperiodic prolonged apnea was associated with swallows, coughing, obstructed breaths, and central apnea. Mimicking apnea of prematurity, these spells were mixed or obstructive. The other patients with apnea had a regularly recurrent pattern and the apneic spell started with a cessation of airflow in late inspiration or early expiration. A recent study[173] in lambs suggests that RSV infection may alter the sensitivity of the laryngeal chemoreceptors locally. Stimulation of these receptors could result in prolonged apnea.

RSV-associated apneic spells are more common in premature babies and young infants, especially in those who have had apnea during the newborn period. Apneic spells usually last only a few days but may be severe enough to require ventilatory support, so infants who develop apnea should be initially hospitalized for cardiorespiratory monitoring.[170] After hospitalization, home respiratory monitoring is not recommended unless the infant has had pre-existing apnea or has neurologic abnormalities.[171] When 48 infants with RSV-associated apnea were followed for the first year of life, Church and colleagues[171] found that the patients were not at risk of subsequent apnea; however, one otherwise healthy infant died at the age of 4 months of aspiration pneumonia.

Infection in Adults

It is now well-documented that RSV infection occurs commonly in adults as well as children. In a family study, 17% of the adults living with infected children also became infected.[50] In adults, RSV infection can be asymptomatic or can induce mild to moderate upper respiratory tract symptoms. In healthy adults, the infection is rarely severe or fatal.[174] The symptoms include fever for 1 to 4 days, nasal congestion, rhinorrhea, sore throat, ear pain, and cough lasting 10 days or longer. The average duration of virus shedding is 5 days.[74] Based on clinical features, RSV infection cannot be differentiated from common cold induced by other etiologic agents. Adults who are immunocompromised, institutionalized, or aged or who have some underlying illness (especially pulmonary disease) may be at risk of severe RSV pneu-

monia. The occurrence of pneumonia in long-term care facilities varies from 5% to 67%, with mortality from 0 to 53%.[28] The chest radiograph usually reveals patchy changes, diffuse consolidation, or interstitial infiltrates. Recently, Guidry and coauthors[175] reported RSV infection in 5 of 11 intubated patients in a medical intensive care unit. Two patients died. Several dual viral infections were recognized, although none of the patients was receiving significant immunosuppressive therapy. In addition, 4 of 48 ward patients became infected. One physician had the virus isolated from his respiratory secretions, a finding which agrees with the hypothesis that hospital personnel usually introduce the illness to the ward. During outbreaks, RSV must be included in the differential diagnosis of fever with evidence of pulmonary infiltrates in immunocompromised adults.[176–178] In one study, 3 of 9 immunocompromised adult patients with RSV infection died.[177] Bronchoalveolar lavage and rapid tests are thus recommended for the diagnosis.[178] Ribavirin may be beneficial in the treatment of severe infections in adults.[174]

High-Risk Children

Children at increased risk from RSV infection include young infants with prematurity,[127, 179] bronchopulmonary dysplasia,[180] congenital heart disease,[181] congenital or acquired immunodeficiency,[89, 182–184] and cystic fibrosis.[185] Premature infants are more likely to have apneic spells, atelectasis/infiltrates, and hyperinflation as seen on the chest radiograph, and may require oxygen therapy and mechanical ventilation. Consequently, these patients need longer hospitalization.[179] Two studies suggested that intubation increases the risk for fatal illness.[122, 175] RSV infection is a major reason for rehospitalization of children with bronchopulmonary dysplasia. In these patients, large numbers of siblings and parental smoking are risk factors, as well as recent need for home oxygen therapy.[180]

Clinicians have been long aware that RSV infection may be particularly severe, long lasting, and fatal in children with congenital immunodeficiency diseases. Although all such patients whom we are aware of have had both T- and B-cell defects, animal studies suggested that T cell–mediated cellular immunity is responsible for terminating RSV infection.[96] No reports of possible increased severity of RSV infection in children with hypogammaglobulinemia have been published. Increased morbidity and mortality have, however, been documented in children undergoing chemotherapy.[183] Pohl and associates[184] reported RSV infection in 17 children who underwent liver transplantation. The clinical symptoms were similar to those in healthy children. Two patients died. The risk factors appeared to be acquisition of infection soon after transplantation and preexisting lung disease. Recently, RSV infection was studied in 10 human immunodeficiency virus (HIV)–infected children who experienced pneumonia and prolonged viral carriage. Two children died, both with concomitant bacterial superinfection.[186]

Congenital heart disease is another well-established risk factor for severe RSV infection. Cardiac function is not depressed in patients with normal hearts who have RSV infection.[187] However, Sreeram and coworkers[188] found tricuspid valve regurgitation in 11 of 21 children with bronchiolitis. MacDonald and associates[181] reported that infants with heart disease and RSV infection needed more treatment in the intensive care unit and more ventilator therapy than those without congenital heart disease. The mortality in infants with heart disease was 37% versus 1.5% in control patients. Even higher mortality (73%) was recorded in patients with pulmonary hypertension. In our experience, these mortality numbers are exceptionally high and probably should not be generalized.

Group A and B Infections

At present it is not clear whether group A and B RSV infections are clinically different. McConnochie and colleagues[189] reported that group A infections were more severe, requiring more mechanical ventilation and producing higher carbon dioxide tension. Furthermore, in a study on 1,209 hospitalized children, those with group A RSV infections more often required intensive care.[190] These observations are in agreement with those from Huntington (West Virginia),[126] England,[191] Argentina,[192] and Uruguay.[193] In contrast, studies in Tecumseh,[43] Boston,[194] Cleveland,[195] and Japan[196] found no differences in the severity of disease relative to group A or B RSV infections.

Secondary Bacterial Infections

Acute otitis media is the most common bacterial complication of RSV infection.[197] Epidemiologic surveillance data show a strong association between RSV infections and acute otitis media. Markedly increased rates of acute otitis media have been recorded during RSV epidemics. About 50% of hospitalized children with RSV infection have or subsequently develop acute otitis media.[198] RSV is the most common virus isolated from the middle-ear fluid, accounting for 41% of 96 virus isolates reported.[197] Although RSV has been frequently found in the middle-ear fluid, there is at present no direct proof that RSV replicates in middle-ear epithelial

cells. Most patients with RSV-associated acute otitis media also have a bacterium in the middle ear.[199] Concomitant RSV infection may explain the poor response to antibiotic therapy in acute otitis media.[200-202]

Systemic bacterial complications of RSV infections are rare in developed countries. The great majority of children with RSV infection have normal values for white blood cell count, erythrocyte sedimentation rate, and serum C-reactive protein concentration.[164] Hall and coworkers[203] observed subsequent confirmed systemic bacterial infections in only 2 of 352 children who had not received previous antibiotic therapy. These children had blood culture–positive streptococcal pneumonia and bronchopulmonary dysplasia. The risk of secondary bacterial infection was markedly increased (11%) in patients who had at least 5 days of parenteral antibiotics. Timmons and coworkers[204] studied retrospectively the charts of 108 children with RSV infection and found 3 with blood cultures positive for *Streptococcus pneumoniae*. Tristram and colleagues[205] reported 4 blood culture–positive *S. pneumoniae* infections in 189 children with RSV infection. Furthermore, 4 adenovirus infections, 1 cytomegalovirus infection, and 1 *Pneumocystis carinii* infection were detected simultaneously with RSV. In addition to these clinical studies, the few autopsy studies that have been reported to date do not support a significant role of concomitant bacterial infections with RSV.[119, 120] These figures probably underestimate the true occurrence of secondary bacterial infections, since blood culture is infrequently positive in childhood pneumonia. Nonetheless, antibiotics have not been shown to be beneficial in the treatment of RSV infections.[206, 207] In a developing country, RSV infection may often be complicated by systemic bacterial infection. In a study of Ghafoor and coworkers[208] in Pakistan, *S. pneumoniae* and *Hemophilus influenzae* were isolated from the blood of 26% of 491 children with RSV infection.

Simultaneous infections with RSV and *Bordetella pertussis* have been demonstrated. In one study,[209] of 29 children with pertussis, 14 also had RSV infection. The temporal sequence of these two infections could not be determined. The symptoms and signs of RSV infection or pertussis alone were similar, as were white blood cell and lymphocyte counts. It is possible that RSV may make young infants more susceptible to pertussis.

A series of recent studies suggested that 30% to 40% of children with RSV infection have concomitant bacterial infection.[33, 34, 210, 211] In all these studies, indirect measures of bacterial infection were used: pneumococcal antigen detection from serum and urine, and measurement of antibody conversion in serum for *S. pneumoniae*, nontypable *H. influenzae*, and *Moraxella catarrhalis*. Further studies are needed to verify the clinical value of these measures of bacterial infections.

Nosocomial Infections

RSV spreads readily among hospitalized populations. Hospital personnel are the leading cause of nosocomial respiratory infection in young children and adults.[212-214] Several epidemics in nurseries, intensive care units, hospital wards, and long-term care facilities have been described. New data show that RSV nosocomial transmission may be more complex than was once believed. Several antigenically different RSV subgroups have been demonstrated during a single hospital epidemic, suggesting that the infection was transmitted from several sources.[179]

Several measures have been found helpful and effective in preventing RSV nosocomial infections. The use of rapid diagnostic techniques permits the detection of infection within hours after the admission. The RSV-infected child should be placed in a single room, if possible. Alternatively, both the patients and staff should be cohorted and careful handwashing protocols observed (Fig 7).[215, 216] RSV is very sensitive to alcohol and detergents because it has a lipid membrane that is destroyed in less than 60 seconds.[217] Recommendations about the use of gowns and masks vary. Hall and Douglas[218] and Murphy and colleagues[219] were unable to show any beneficial effects for their use. In contrast, LeClair and associates[220] found that the use of gowns and gloves substantially reduced the nosocomial transmission of RSV infection, after specific intervention to monitor compliance was carried out by the nursing staff. In addition to these procedures, use of goggles covering the eyes and nose[128] and limiting visitors (no siblings, no visitors with respiratory symptoms except parents wearing a mask)[221] have been demonstrated to reduce the transmission of RSV in hospital settings.

Mortality

The mortality associated with primary RSV infection in otherwise healthy children is estimated to be 0.005% to 0.020%.[222] In hospitalized children, mortality rates are estimated to be from 1% to 3%.[2] Considerably higher mortality rates in children with cardiopulmonary abnormalities and in immunosuppressed subjects (see High-Risk Children) have been suggested.

Due to the common occurrence of RSV infection, even a low mortality rate may have marked impact

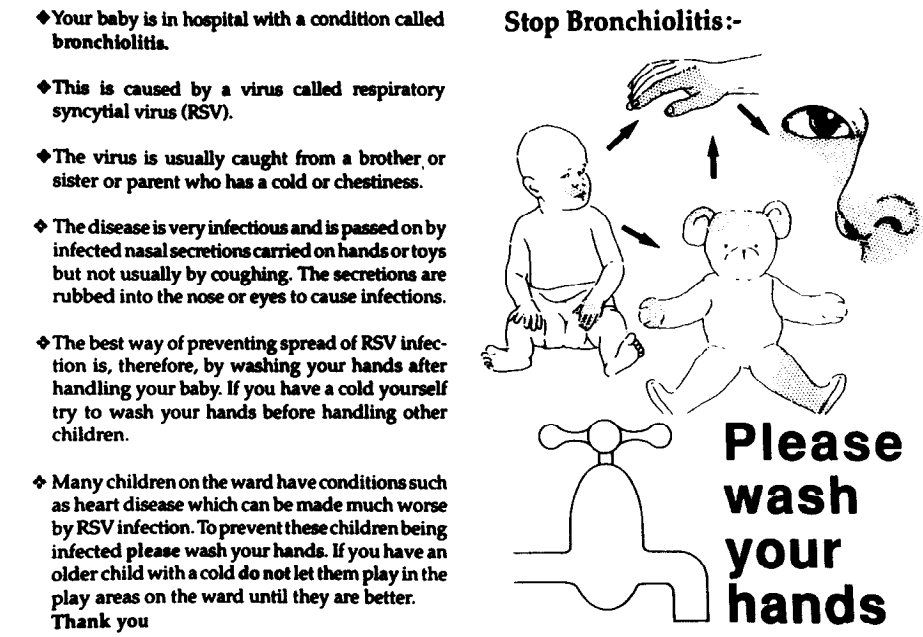

FIGURE 7
Information leaflet given to parents. (From Isaacs D, et al: *Arch Dis Child* 1991; 66:227–231. Used by permission.)

on the total mortality of young children. Anderson and colleagues[39] compared the temporal patterns of respiratory viral isolations from ten laboratories in the United States with that of deaths of children. They found that RSV isolations were clearly associated with the respiratory deaths of children 1 to 11 months old. Influenza virus infection was associated with the deaths of children 24 to 59 months old. The investigators estimated that between 90 and 1,900 deaths of children less than 1 year old may be associated with RSV each year.

A significant correlation has been shown to exist between the occurrence of sudden infant death syndrome (SIDS) and RSV infections.[39, 223] RSV has been demonstrated in the lungs of up to 25% of infants who died from SIDS.[224] Prolonged apnea, which is a major sign of newborn RSV infection, may explain some of these deaths. At present, however, the role of RSV in SIDS is not fully understood.

Immune Response

RSV infection induces both serum and mucosal IgM, IgA, IgG, and IgE antibodies. Primary RSV infection induces IgM response in 5 to 10 days, depending on the age of the patient. Meurman and colleagues[225] found an IgM response in 73% of the 26 patients with RSV infection, including 63% of the infants less than 6 months old, and 100% of the patients 1 to 2 years old. Welliver and associates[226] also found a lower IgM response in patients less than 6 months old. IgM antibodies persist, usually, for 1 to 3 months. However, Popow-Kraupp and coworkers[227] found IgM antibodies against RSV to remain detectable at least 1 year, using immunoblot analysis.

RSV-specific IgG antibody response can be detected in most patients; it reaches maximum values in 20 to 30 days after the onset of symptoms.[225, 226] Again, lower responses in young infants have been reported.[228] IgG response occurs mainly in IgG1 and IgG3 subclasses, indicating the antigenic nature of the protein moieties of the F and G proteins of RSV.[229] One year after the primary infection occurs, RSV-specific IgG levels appear to decline to low levels. After re-infection, a booster effect is noted, with high titers of IgG detectable within 5 to 7 days.[226]

The serum IgA response to RSV infection occurs several days later than IgM and IgG responses.[225] Interestingly, Meddens and coworkers[228] found an IgA response most often in the younger age group, suggesting that it may have diagnostic value. IgA can be found free and cell bound in nasopharyngeal secretions of patients with RSV infections. Free anti-RSV IgA appears within 2 to 5 days after infection and peak titers are obtained between 8 and 13 days.[80] The nasopharyngeal IgA response is greater in children older than 6 months. Furthermore, nasal secretions contain free RSV-specific IgM, IgG, and IgE and cell-bound IgM, IgG, and IgE during RSV

infection.[80] A mucosal immune response to RSV has also been demonstrated by RSV-induced antibody response in vitro in tonsillar lymphocytes.[230]

Several studies have demonstrated specific antibody responses to major RSV structural proteins.[45, 231–233] Hendry and coworkers[232] showed that the antibody responses to the F protein of RSV were cross-reactive with both RSV strains tested, whereas antibody responses to the G protein were subgroup specific. Similar findings were reported by Muelenaer and coauthors,[45] who studied group-specific antibody responses to primary and secondary RSV infections. These observations suggest that primary and secondary infection with group A viruses can induce cross-reactive neutralizing antibody responses to group B viruses.

Siber and coworkers[79] recently studied different RSV antibody assays to detect IgG with high virus-neutralizing and animal protective activity. Results of direct ELISAs using purified F protein, G protein, or RSV-infected cell lysate, two competitive ELISAs with RSV-neutralizing antibodies to F2 or F3 epitopes of F protein, plaque reduction neutralization assays, and microneutralization assays were compared. Interestingly, they found a low level of correlation between the assays, suggesting that each assay may measure functionally different populations of RSV antibodies.

RSV infection induces specific cell-mediated immune responses including lymphocyte transformation, cytotoxic T-cell response, and antibody-dependent cellular cytotoxicity response. These are discussed in the section Pathogenesis.

Diagnosis

During an outbreak, diagnosis of RSV infection can often be assumed on the basis of the signs and symptoms of infection and the age of the patient. Specific viral diagnosis is necessary for the cohorting of hospitalized patients, in severely ill patients needing intensive care, and in high-risk patients. Specific diagnosis also is indicated if a patient is being considered for antiviral chemotherapy or has failed antibiotic therapy.

A properly collected and transported mucus sample from the nasopharynx is crucial in the diagnosis of RSV infection. It has been shown that recovery of the virus is highly dependent on the training and interest of the personnel collecting the samples.[234] Nasopharyngeal specimens can be obtained by swabbing, washing, or aspiration. Although still in common use, nasopharyngeal and pharyngeal swabs give the worst results.[235] Nasal wash and nasopharyngeal aspiration are both recommended as the methods of choice.[2, 44] In nasal washing, 3 to 7 mL of phosphate-buffered saline solution in a rubber bulb is squeezed into the nostril and then recollected by releasing the bulb. Almost all the saline solution instilled can be recovered.[2] Nasopharyngeal aspiration specimens are collected by a disposable catheter and mucus extractor (e.g., Vygon, Ecouen, France) connected to a mechanical vacuum. Alternatively, a no. 5 French nasogastric feeding tube connected to a syringe has been used for aspiration.[236] The catheter is transported through a nostril into the nasopharynx until it reaches the backwall. After the vacuumer is activated, the catheter is slowly drawn out, aspirating the secretions. The volume of the specimen collected is usually 0.5 to 2.0 mL. Samples for virus culture should be placed in the proper transfer medium and kept on ice until processed. The clinical specimens should be collected as early as possible after the onset of symptoms. The recovery of the virus decreases markedly after 5 to 7 days. In two studies, in only about 50% of the cases of documented RSV could RSV still be detected after the symptoms had lasted longer than 7 days.[35, 237]

During the last 5 to 6 years, an avalanche of studies on different RSV diagnostic methods have been reported. The different laboratory techniques are thoroughly discussed in several recent reviews.[3, 4, 235] RSV infection is usually diagnosed by detecting the virus by tissue culture infectivity or by demonstrating viral antigen by immunoassay in the nasopharynx. After the acute phase of the illness, the diagnosis can be made by demonstrating a significant increase of specific antibodies in paired serum samples. In addition, nucleic acid detection and polymerase chain reaction methods have been described, but they are currently available only in certain research laboratories.[95, 238–240]

Rapid detection of viral antigen by immunoassay is at present the most suitable single method to demonstrate RSV infection. Several commercial kits for ELISAs or membrane enzyme immunoassays have been developed. For the ELISA procedure, a polystyrene microtiter well, a bead, or a nitrocellulose membrane is coated with anti-RSV antibody. The antigen in the clinical sample is captured by the antibody and this complex is captured by a second specific antibody, which is labeled (direct assay) or followed by a labeled anti-species antibody against the second one (direct assay). Peroxidase and alkaline phosphatase are most commonly used as labels. The assay time is 2 to 5 hours. Two membrane enzyme assays do not require any special equipment and take only 15 to 20 minutes. The sensitivity and specificity of ELISAs and membrane immunoassays range usually from 80% to 90% (Table 4).[241–250] The

TABLE 4
Rapid Detection of Respiratory Syncytial Virus Antigen in Nasopharyngeal Specimens Compared to Viral Culture (Studies From 1988 to 1991)

Commercial Test*	Reference	No. of Positive Cultures	Sensitivity (%)	Specificity (%)
Kallestad EIA (75 min)	Johnson and Siegel[241]	133	87	88
	VanBeers et al[242]	124	74	76
	Wren et al[243]	93	76	90
	Ahluwalia and Hammond[244]	61	79	98
Ortho EIA (5 hr)	Thomas and Book[245]	26	88	87
	Ahluwalia and Hammond[244]	61	95	99
	Christensen and Flanders[246]	22	86	78
Directigen (15 min)	Freymuth et al[247]	103	91	98
	VanBeers et al[242]	124	88	76
	Rothbarth et al[248]	38	76	73
	Halstead et al[249]	57	76	80
TestPack (20 min)	Thomas and Book[245]	55	91	95
	Rothbarth et al[248]	38	92	97
	Wren et al[243]	93	92	91
	Halstead et al[249]	57	94	100
	Swierkosz et al[250]	70	100	95

*In parentheses are the times required to perform the tests.
EIA = enzyme immunoassay.

tests are simple and inexpensive and do not require a highly experienced technician. Furthermore, the nasopharyngeal samples can be sent by mail or kept overnight in a refrigerator. The tests measure free antigen, so the samples do not need to have intact epithelial cells. Monoclonal antibodies for ELISA are also available for influenza A and B viruses; parainfluenza type 1, 2, and 3 viruses; and adenovirus. Currently, the most sensitive antigen detection method is time-resolved fluoroimmunoassay (TR-FIA), which requires only 1 hour of incubation and is also available for several other viruses.[35, 44]

If the number of samples per day is limited, direct or indirect immunofluorescent tests may be an alternative for ELISA. They have comparable sensitivity and specificity and monoclonal antibody reagents are available commercially.[235] As much as 25% of the nasopharyngeal samples may, however, be inadequate for immunofluorescence studies due to the lack of intact cells.[235] Furthermore, special ultraviolet light microscope and well-trained microscopists are needed.

Although rapid antigen detection tests are now recommended as a primary test to detect RSV infection, detection of infectious virus by cell culture still remains the standard procedure. Optimally, the procedure is performed on several cell lines at the same time. Most often Hep-2, HeLa and Vero cells are used. The susceptibility of cell lines to RSV must be monitored. The typical cytopathic effect is usually seen in 2 to 7 days, but may take as long as 21 days.[235, 246] The cell culture infectivity is markedly improved by the shell vial technique: a procedure involving short centrifugation of the sample and detection of virus antigen by peroxidase staining[251] or immunofluorescence[236] after 16 to 48 hours of culture. In addition to the short assay time, the sensitivity is increased.

The cell culture assay is necessary because it also will detect other, often unexpected viruses; furthermore, some species (e.g., rhinoviruses) cannot at present be detected by antigen tests. Several other viruses may occur in the community concomitantly with an RSV epidemic. Furthermore, some specimens may show positivity in cell culture and negativity in antigen detection tests and vice versa.[235] The disadvantages of cell culture are that the cultures are difficult to maintain, samples need rapid processing, identification needs skill and experience, and the results may come too late to affect the decision-making process to patient management.

Serologic tests provide immunologic evidence of infection after the acute phase of the disease. They are especially necessary in clinical research, when the etiologies of different infections are studied. Several studies have shown the complement fixation test to be insensitive, especially in very young children.[3, 4] It has been replaced by more sensitive assays of IgG-specific antibodies measured by enzyme immunoassay.[237]

Treatment

Supportive Care

Many hospitalized patients with RSV infection are hypoxemic. Although respiration and heart rates are routinely monitored, they may be unreliable predictors of hypoxemia. Pulse oximetry is recommended for all young infants with RSV-induced lower respiratory tract infection.[130, 136] Patients having oxygen saturations lower than 95% usually require hospitalization.[252] Supplemental humidified oxygen therapy is the cornerstone of the treatment. The majority of patients respond well to 40% oxygen. Continuous monitoring of blood gases is necessary. Acute respiratory acidosis (pH < 7.25, arterial carbon dioxide pressure [$Paco_2$] > 60 mm Hg), severe hypoxemia (arterial oxygen pressure [Pao_2] < 60 mm Hg in 40% oxygen) that is unresponsive to oxygen administration, and recurrent prolonged apnea are indications that ventilatory support therapy may be required.[253–256] The mean duration of mechanical ventilation has been reported to be 4 to 9 days.[254, 255] Mechanical ventilation should be discontinued when the patient is able to maintain a Pao_2 of at least 70 mm Hg and $Paco_2$ of at least 45 mm Hg. Supplemental oxygen is recommended as long as oxygen saturation is lower than 95%.[256] Extracorporeal membrane oxygenation has been successfully used when maximal ventilatory support has failed to maintain adequate ventilation.[257]

Intravenous hydration has also been recommended. However, two recent studies reported markedly elevated plasma antidiuretic hormone (ADH) levels in children with bronchiolitis.[258, 259] Hypertranslucency on chest radiograph, hypercapnia, and mechanical ventilation are associated with elevated plasma ADH levels. The authors of these studies stressed that in spite of normal serum sodium levels, the patient may be overloaded with fluids. Careful monitoring of body weight in addition to plasma electrolyte concentrations is thus necessary, and in some cases, restricted fluid intake may be indicated.

Mist treatment and physiotherapy were once standard supportive therapies for bronchiolitis. At present there is evidence that they may do more harm than good.[260] Frequent aspiration of excessive nasopharyngeal mucus may be necessary in some patients to relieve breathing and feeding difficulties.

Bronchodilator Drugs

The use of bronchodilators in the treatment of bronchiolitis and wheezy bronchitis in young infants has been controversial. Earlier studies have suggested little or no beneficial effects of isoprenaline, epinephrine, salbutamol (albuterol), or theophylline.[260–263] Several recent studies, however, suggested that bronchodilators may have a beneficial effect in some patients with bronchiolitis. Subcutaneous epinephrine was found effective in the treatment of wheezing in 63% of patients less than 12 months old and in 92% of those 12 to 24 months old when respiratory rate, wheezing, and retractions were used as clinical criteria.[264] Mallory and associates[265] studied 14 mechanically ventilated infants with RSV bronchiolitis. They showed that isoetharine or isoproterenol aerosols significantly increased the maximum expiratory flow rate at 25% (MEF_{25}) of forced vital capacity (FVC). Schuh and colleagues[266] demonstrated significant improvements in the accessory muscle score, respiratory rate, and oxygen saturation after two doses of nebulized salbutamol in 40 infants with bronchiolitis. A positive response to such therapy was also shown by children less than 6 months old. In a double-blind, placebo-controlled study Klassen and coworkers[267] found improvement in clinical scores but not in oxygen saturation. Significant improvement in lung function was observed in wheezy infants after 15 minutes of inhalation of salbutamol compared to placebo.[268] Studying respirosonography in infants with bronchiolitis, Tal and coworkers[269] showed that nebulized salbutamol induced a marked decrease in the duration of expiratory wheezing in 7 of 16 infants studied. Recently, nebulized metaproterenol was demonstrated to be effective in 40% of those aged 12 months and younger and in 52% of those 24 months and older with acute wheezing.[270] These findings suggest that nebulized bronchodilator therapy should be tested in children with bronchiolitis. However, the response should be carefully monitored, because in some patients salbutamol may induce a fall in oxygen saturation.[262, 263] High doses of nebulized salbutamol (0.15 mg/kg) may be needed, as shown in older children with asthma.[271]

Corticosteroids

Five earlier studies on the use of systemic corticosteroids in the treatment of acute bronchiolitis showed no beneficial effects.[261, 272] In a report in 1970, the American Academy of Pediatrics concluded that "there is no scientific basis for the routine administration of corticosteroids in bronchiolitis."[273] This conclusion is still valid today. Recently, there has been a resurgence in studies of corticosteroids in bronchiolitis. Tal and coworkers[274] showed in a small number of patients that intramuscular dexamethasone and salbutamol used together, but not separately, had favorable effects on the clinical course of children with acute wheezing associated with upper respiratory tract symptoms. However,

these findings could not be confirmed by Springer and coworkers,[272] who studied only patients with the first attack of bronchiolitis.

Inhaled steroids are now the main treatment of childhood asthma. Carlsen and colleagues[148] showed that nebulized beclomethasone for 8 weeks markedly decreased the recurrent severe wheezing attacks after bronchiolitis. Furthermore, Bisgaard and associates[149] demonstrated that budesonide inhaled for 12 weeks from a pressurized aerosol through a spacer with a face mask significantly reduced the frequency of recurrent wheezing in children 11 to 36 months old. Recently, Noble and coworkers[151] confirmed the beneficial effects of inhaled budesonide in children under 18 months old with chronic wheezing. In Europe, inhaled steroids are already a standard treatment for recurrent wheezing after bronchiolitis, but further studies are needed to establish the dosage, duration, and method of delivery as well as possible long-term adverse effects.

Ribavirin

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamine) is an analog of guanosine and inosine. It has a broad antiviral spectrum, and is effective not only against RSV, but also in vitro against measles, parainfluenza, and influenza viruses.[275]

The drug is delivered as an aerosol by a special mist generator for 18 to 20 hours daily for 3 to 5 days. Recently, high-dose, short-duration therapy has been studied with promising results.[276] Given orally, ribavirin may induce a reduction in red blood cell counts and an increase in bilirubin levels. Table 5 shows the indications for use of ribavirin. The use of ribavirin is generally accepted for those infants with pre-existing moderate to severe cardiopulmonary disease and severely immunosuppressed patients. Pohl and colleagues[184] studied RSV infections in pediatric liver transplant recipients. Infections within 20 days after transplantation and during exaggerated immunosuppression were most severe and were considered indications for ribavirin therapy. Ribavirin has not been recommended for patients with mechanical ventilation support, because the drug may precipitate within the ventilator apparatus.[277] However, Smith and coworkers[256] recently reported the safe and effective use of ribavirin in 14 young infants who needed mechanical ventilation for severe RSV infection.

TABLE 5
Indications for Use of Ribavirin in Respiratory Syncytial Virus Infections*†

Use as early as possible in patients with
Severe cyanotic congenital heart disease
Severe bronchopulmonary dysplasia
Postoperative cardiac surgery
Use to avoid intubation in patients with
Moderate cyanotic congenital heart disease
Symptomatic bronchopulmonary dysplasia
Cystic fibrosis
T-cell immune defects
Use in any child who is consistently severely hypoxic ($Pa_{O_2} < 60$ mm Hg in room air, $Pa_{CO_2} > 40$ mm Hg)

*Modified from the recommendations of the Committee on Infectious Diseases, the American Academy of Pediatrics: *Pediatrics* 1987; 79:475–478; and from McIntosh: *Pediatr Rev* 1987; 9:191–196.
†Further studies are needed to clarify the role of ribavirin treatment in intubated patients requiring mechanical ventilation.

Available data based on eight double-blind, placebo-controlled trials of the efficacy of ribavirin published during the last 9 years are summarized in Table 6. Of a total of 233 patients studied, 116 received ribavirin. Some benefits were observed in the clinical recovery phase, oxygen saturation, and viral shedding. Recently, it was suggested that early ribavirin therapy may reduce the morbidity of RSV infection in children with bronchopulmonary dysplasia or with congenital heart disease.[283] Furthermore, the study in mechanically ventilated infants showed that ribavirin treatment reduced the time of mechanical ventilation, oxygen therapy, and hospital stay. In spite of these observed benefits, no significant reduction in overall cost for the care of patients with severe RSV infection was obtained.[256]

Ribavirin therapy is well tolerated and no acute toxicity has been reported. However, concern about possible long-term harmful effects, suppression of immunity, and possible risk to caretakers have been expressed. Use of surgical gloves and masks is recommended to minimize the potential exposure to the staff. Nurses known to be pregnant should avoid taking care of the patients receiving ribavirin therapy.

The use of ribavirin in previously healthy infants with RSV infection is a topic of great controversy.[285, 286] The primary argument against use of the drug is that in the great majority of infants, even in those with severe lower respiratory tract RSV infection, the signs and symptoms of illness resolve uneventfully with supportive therapy alone within a few days. In addition, the clinical benefit appears to be modest at best. Most studies are based on a limited number of patients, have not included double-blind, placebo controls, and often lack objective criteria when estimates of clinical efficacy are presented. No effects have been noted with respect to mortality, need for intensive care, and subsequent use of mechanical ventilation. In addition, the possible risks of exposure of health care personnel to ribavirin is still of concern. In spite of the shortage of

TABLE 6
Double-Blind, Placebo-Controlled Studies on Ribavirin in the Treatment of Respiratory Syncytial Virus Infection

	No. of Patients	Underlying Illness	Criteria to Evaluate Efficacy	Response at the End of Therapy	Ribavirin/Placebo
Hall et al[278] (1983)	33	None	Clinical score	Improved	0.8/1.7*
			Oxygen tension	Improved	62 mm Hg/56 mm Hg
			Viral shedding	Improved	2.9 days/4.3 days
Taber et al[279] (1983)	26	None	Clinical score	Improved	0.6/1.3†
			Viral shedding	No change	
Hall et al[280] (1985)	26	BPD	Clinical score	Improved	55%/29%‡
		CHD	Oxygen tension	Improved	73 mm Hg/58 mm Hg
		None	Viral shedding	Improved	
Barry et al[281] (1986)	26	None	Clinical score	Improved	
			Heart rate/min	Decreased	39/31
			Respiratory rate/min	Decreased	20/16
			Viral shedding	No change	3.5 days/4 days
Rodriguez et al[282] (1987)	30	BPD	Clinical score	Improved	0.6/1.2*
		None	Oxygen saturation	Improved	
			Viral shedding	No change	
Groothuis et al[283] (1990)	47	BPD	Clinical score	Improved	1.7/2.2§
		CHD	Oxygen saturation	Improved	91%/88%
			Need for mechanical ventilation	No differences	
			Need for ICU	No differences	
			Need for oxygen	Decreased	
Edelson[284] (1990)	17	BPD	Tachypnea	No difference	
		CHD	Oral feeding	No difference	
			Hypoxemia, days	No difference	
			Need for supplemental oxygen	Decreased	2.2 days/5.6 days
			Need for mechanical ventilation	Decreased	0.5 days/2.5 days
Smith et al[256] (1991)	28	BPD	Need for mechanical ventilation	Decreased	4.9 days/9.9 days
		CHD			
		None	Need for supplemental oxygen	Decreased	8.7 days/13.5 days
		All mechanically ventilated	Need for hospital stay	Decreased	13.3 days/15.0 days
			Hospital bill	$68,067/$77,666	

BPD = bronchopulmonary dysplasia; CHD = congenital heart disease; ICU = intensive care unit.
*Mean illness severity scores at the end of therapy. A score of 0 is normal and 4, most severe.
†0 is normal and 3, most severe illness.
‡Mean percent of improvement of clinical score.
§0 is patient's normal baseline value and 10, the worst severe illness.

our knowledge, however, ribavirin use has expanded, especially in the United States. In 1992, it was estimated that 200,000 patients with RSV infection have been treated with ribavirin. In Turku, Finland, during the 1991 to 1992 epidemic, 136 patients with RSV infection were hospitalized and no patient received ribavirin therapy. In contrast, in Galveston, Texas, 66 patients were admitted to a hospital and 14 were treated with ribavirin. Interestingly, a comparative study was performed in two centers in the United States, one using and the other one not using ribavirin. During three RSV seasons, 215 patients fulfilled the criteria of the American Academy of Pediatrics for ribavirin therapy; 108 patients were treated in one center and no one in the other. There were no differences in the need for oxygen therapy, need for mechanical ventilation, length of hospitalization, and mortality between the ribavirin-treated group and the group not treated with ribavirin.[287,288] The effect of ribavirin therapy on hospital expenses is enormous since a single day of treatment costs $487. As stated by many authors, it is clear that more carefully planned and performed studies are needed to delineate the indications of ribavirin in the treatment of severe RSV infections in previously healthy infants.

Intravenous Gamma Globulin

Studies in experimental animals and human infants suggested that RSV antibodies given in intravenous immunoglobulin (IVIG) may shorten the course and

decrease the severity of RSV infection.[289] Hemming and coworkers[77] showed in a double-blind, placebo-controlled study that a single dose of 2 g of IVIG administered to children with RSV pneumonia or bronchiolitis significantly reduced the nasal shedding of RSV and improved the oxygen saturation, compared to placebo. The efficacy of IVIG is dependent on the neutralizing titer of anti-RSV antibody.[79] Recently, a humanized monoclonal antibody to RSV was shown to be highly effective in vitro and in vivo.[290] Further clinical studies with high-titer products are needed.

Antibiotic Therapy

Antibiotic therapy is given to at least 40% to 50% of patients hospitalized with RSV infections.[203, 291] Most often the indications include acute otitis media or possible bacterial-type pneumonia (see Secondary Bacterial Infections). However, in most patients, no concomitant bacterial infection can be demonstrated and there are no clear-cut indications for antibiotics in RSV infection in developed countries. Antibiotics are often ordered, however, because of the young age of the patients and difficulties in ruling out possible bacterial infection. Carlson and Orstavik[291] showed that the active use of rapid RSV diagnosis reduced the use of antibiotics from 80% to 40%. Two randomized studies demonstrated that routine antibiotic therapy has no benefits in the treatment of bronchiolitis. In the study by Field and colleagues,[206] use of antibiotics such as ampicillin did not influence the outcome of bronchiolitis. The authors concluded that the antibiotics were used more to treat the physician's peace of mind than the patient's disease. Friis and coworkers[207] studied over 100 children with bronchiolitis or pneumonia. Ampicillin or penicillin treatment did not change the clinical course of the illness. Mastoiditis developed in one patient in the control group. It can thus be concluded that antibiotics are used often unnecessarily in the treatment of RSV infections. House staff should have clear instructions for the use of antibiotics in patients with RSV infections.

Prevention

Vaccines

At present no safe and effective vaccine against RSV infection is available. Several different kinds of vaccines have been developed and some even tested in clinical trials.[292–294] A formalin-inactivated RSV candidate vaccine studied in the 1960s induced virus-specific–neutralizing and complement-fixing antibodies. Paradoxically, however, during subsequent RSV infection a more severe pulmonary disease developed. Therefore, attenuated live-virus vaccines derived from wild-type virus grown in human diploid cells were developed. In clinical studies these vaccines were shown to be ineffective.

By passaging RSV at 26°C, attenuated cold-adapted RSV vaccine was developed but the vaccine induced mild respiratory disease in vaccinees. Temperature-sensitive mutants of RSV (virus is able to replicate at 37.0°C but not in higher temperatures) have also been tested. One and two mutant vaccines appeared to be either genetically unstable, pathogenic, or overattenuated with poor infectivity. A triple mutant RSV induces detectable anti-F and anti-G antibodies in adult volunteers and apparently has greater genetic stability than the earlier mutants.[295] In experimental animals, recombinant vaccinia viruses or baculoviruses containing genes for F and G proteins have proved to be safe and effective. Finally, synthetic peptides of F protein have been studied as candidate vaccines. Promising results have been obtained with an immunoaffinity purified F protein vaccine, which is now undergoing clinical studies.

The development of effective and safe RSV vaccine has been difficult, since the vaccine needs to be given as early as the age of 1 month in order to have a significant impact on the frequency of disease. Unfortunately, maternally derived RSV antibodies exist at this time and may reduce its efficacy.

Intravenous Gamma Globulin

Animal studies have demonstrated that intravenous gamma globulin may prevent RSV-induced lower respiratory tract infection. Furthermore, favorable effects have been shown when IVIG was used in the treatment of RSV infection in human infants.[77] Groothuis and associates[78] studied IVIG in the prevention of RSV infection in 23 high-risk infants. These children with bronchopulmonary dysplasia or congenital heart disease received IVIG, 500 to 750 mg/kg, monthly from the age of 8 to 12 months. During the follow-up of 2 years, 12 children developed RSV infection. One child died; the other 11 infections were mild. The authors calculated that IVIG at 750 mg/kg, with an RSV titer of 1:4,000 or greater, would be effective to prevent RSV infection if it is given monthly during the epidemic season. It is important to note that microneutralization assay should be used when screening plasma samples for highest protective activity.[79] Further trials are under way to clarify the role of IVIG in the prevention of RSV infection.

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