Overview of bronchiolitis

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ABSTRACT

Respiratory syncytial virus (RSV), a nonsegmented, single stranded ribonucleic acid virus, infects one-half of all infants within the first year of life. Respiratory syncytial virus possesses pathogenetic qualities that may be attributed to the interplay of viral and host-specific factors including virus strains of different virulence, size of the inoculum, family history of asthma or airway hyper-reactivity and immunologic anomalies of the host. Inflammatory cell recruitment and activation occur in response to RSV infection of epithelial cells. Epithelial cells initiate the inflammatory response to RSV by elaborating a wide variety of cytokines and chemokines that trigger further inflammatory responses. Treatment of RSV in infants with bronchiolitis is complicated due to the multifactorial nature of this infection. Treatment of RSV bronchiolitis rests primarily on supportive care with oxygen and fluid management. Other therapies commonly used include bronchodilators, corticosteroids and ribavirin, where considered appropriate. Although oxygen administration and judicious fluid replacement are the only interventions proved to be of reliable benefit to infants with bronchiolitis, newer studies support a role for adjunctive therapies aimed at relieving airway obstruction, especially when administered very early in the course of the illness or given to infants with more severe disease.

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Bronchiolitis is the most common lower respiratory tract infection in infants; respiratory syncytial virus (RSV) being by far the most common cause of viral lower respiratory tract infection in infants and young children. Although infection with RSV occurs in most individuals within the first few years of life, episodes of RSV-positive pneumonia or bronchiolitis can be life threatening in very young children.[1] Viral bronchiolitis is the most common cause for hospitalization among infants (<6 months of age) who reside in developed countries.[2] This paper is several folds: (1) to discuss the epidemiology of RSV and the population at risk to develop RSV infections; (2) to review the various theories underlying the pathogenesis for virus-induced childhood RSV respiratory illness and severity of disease; and (3) to explore current theories on the immunology of postbronchiolitic wheezing and the potential association of RSV infection with the development of extrinsic childhood asthma.

Etiology. Respiratory syncytial virus is categorized within the family of Paramyxoviridae and the genus of Pneumovirus.[2] Infection with RSV occurs via transmission of respiratory secretions or by direct contact with contaminated objects.[3,4] Respiratory syncytial virus is an enveloped, medium sized virus (120 to 300 nm) consisting of a single negative strand of nonsegmented ribonucleic acid (RNA). The fact that RSV is non-segmented is considered important as the virus does not reassort with other viruses. In contrast, the segmented viruses, namely influenza and rotavirus, have a much greater likelihood of reassortment, especially with viruses from other species.[5] Reassortment can lead to potential changes in the genetic composition of a virus, thereby making the virus either more virulent or more resistant to existing serum antibody in humans and to some cell-mediated immune responses. Respiratory syncytial virus has 2 major glycosylated surface immunogens, the fusion (F) and the attachment (G) glycoproteins, both of which

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are associated with the envelope of the virus. Those immunogens play a key role in infectivity and are the antigens against which neutralizing responses are directed. The G protein mediates attachment of the virus to target epithelial cells in the host, whereas the F protein facilitates fusion of the virus lipid membrane with the cellular lipid membrane, permitting insertion of the RNA into the host cell. The F protein also promotes fusion of uninfected host cells, leading to the formation of syncytia. Respiratory syncytial virus can infect host cells with only the F protein; the G protein appears to be less vital for the infectivity process.[6] Two subtypes of RSV (A and B) are recognized. These subtypes differ primarily on variations in the structure of their G-protein. Strains of both subtypes circulate simultaneously during outbreaks, although the proportion of each varies widely. The clinical significance of subtype differentiation remains uncertain with no major difference in virulence between the 2-subtype strains.[7, 8]

Epidemiology. Virtually, all children have been exposed to RSV by their second birthday and/or have developed antibodies to RSV by the age of 3 years.[9,10] Of infants with bronchiolitis (especially severe forms), 70% of episodes can be attributed to infection with RSV.[11] Transplacentally, transmitted anti-RSV antibody, when present in high concentration, has some protective effect. This probably accounts for the low frequency of severe infections in the first 4-6 weeks of life, except in infants born prematurely who receive less than a full complement of maternal immunoglobulins. Nevertheless, serum antibody is not fully protective, and the age at which an infant undergoes first infection depends also on the opportunities for exposure. Unfortunately, infection with RSV does not grant complete immunity. Reinfections are common and may be experienced throughout life. Reinfection occurs at a rate of 10-20% per epidemic throughout childhood.[11] Respiratory syncytial virus is distributed worldwide and appears in yearly epidemics.[12] In temperate zones outbreaks usually occur in the winter or spring and last 4-5 months.[13] During the remainder of the year, infections are sporadic and uncommon. In the Northern Hemisphere, epidemics usually peak in January, February, or March, but peaks have been recognized as early as December and as late as June.[14] In the tropics, the epidemic pattern is less clear.[15] Because of the prevalence and morbidity associated with bronchiolitis, the economic burden placed on health care services is substantial. According to a recent estimate on the economic burden of asthma in the United States of America (USA), the cost of treating this disease approaches $13 billion dollars annually, in 19981.[16] In fact, viral bronchiolitis is the most common cause for hospitalization among infants (<6 months of age) who reside in developed countries.[17] Calculations based on hospital admissions in the USA and United Kingdom yield a ratio of 1-3 infants hospitalized with bronchiolitis or pneumonia for every 100 primary infections with the virus.[18]

Population at risk. Bronchiolitis and pneumonia resulting from RSV are more common in boys than in girls by a ratio of approximately 1.5:1. Young male patients appear to experience more severe disease than their female counterparts. Racial factors make a little difference. Environmental factors of crowding (namely 2 or more children sleeping in the same room with the infected child) and passive exposure to tobacco smoke are associated with the development of more severe illness.[10] Infants who have not breast-fed appear to be at greater risk for developing severe RSV infections. However, it is uncertain whether these children are from a lower socio-economic population or whether some actual component of the breast milk protects against severe illness. Children with underlying heart disease, in particular those conditions complicated by pulmonary hypertension, or chronic lung disease, as well as prematurity, are at increased risk for acquiring more severe RSV infections, as evidenced by their increased rates of intensive care unit admissions and need for mechanical ventilation.[19, 20]

Prematurity and RSV infection. A fundamental risk factor for acquiring RSV infection among premature infants is an immature immune system. Both the quantity and the qualitative function of neutrophils and complement differ significantly between the premature infant and his or her full term counterpart.[21] Although the T cell line appears to function normally in most preterm infants, an imbalance in chemokine and cytokine regulation may occur, predisposing the prematurely born child to infection with viral pathogens.[22] Incomplete transfer of maternal antibodies represents another risk factor for RSV among premature infants.[23] It is, also, well appreciated that in premature infants the respiratory system is underdeveloped.[24] Both the anatomy and physiology of the lungs differ between premature infants and those born at term. Lung volume measured in premature infants born at 30 weeks gestation is -25 ml compared with 150-200 ml in full term infants. In addition, premature infants have fewer alveoli and narrower alveolar diameters (32 µm versus 150 µm). Based on a series of studies,[25] -20% of hospitalizations because of RSV involve preterm infants (range, 12 to 27%). In the prospective Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) study of 1516 Canadian children hospitalized with lower respiratory infection caused by RSV, prematurity was a factor in 20% of the cases.[26,27] Premature infants have relatively high rates of RSV hospitalization during the first year of life, with no

discernible differences for those born <28 weeks gestational age, 28-32 weeks gestational age or 32-35 weeks gestational age. During subsequent years, the need for hospitalization declines to rates similar to those in children at low risk who are <1 year of age.[28,29]

Congenital heart disease (CHD) and RSV infection. In a Canadian study, by Navas et al,[30] including 260 children with CHD hospitalized with RSV bronchiolitis, 33% required intensive care, 19% received mechanical ventilation, and 3.4% died. Altman et al[31] reviewed the course of 56 RSV-infected patients with CHD. The average length of hospitalization was 7.4 days, and 25% of patients required intensive care. The average age at admission was 16 months, and 40% of patients were older than 12 months, indicating that an increased risk of RSV hospitalization can extend into the second year of life for children with certain uncorrected or incompletely repaired cardiac abnormalities. Fixler[32] noted that mortality from RSV infection in infants with CHD declined between the 1970s and the mid-1990s from 37% to 3%, in large part, because of improvement in inpatient management in the intensive care unit, as well as advances in cardiac surgery in young children.

Cystic fibrosis and RSV infection. In a 2-year prospective study, Wang et al[33] followed 49 patients with cystic fibrosis and 19 normal sibling controls without cystic fibrosis. The mean number of respiratory illnesses in siblings (1.7 per year) was significantly lower than for those with cystic fibrosis (3.7 per year; $p<0.001$). Respiratory syncytial virus accounted for ~18% of the symptomatic infections identified in the cystic fibrosis group. No controls were hospitalized for respiratory illness, whereas 16 of 41 (39%) hospitalizations among cystic fibrosis patients were the result of viral respiratory illness, with an average length of hospitalization of 14 days. Abman et al[34] followed 48 children with cystic fibrosis to determine the frequency of RSV-induced hospitalization and to evaluate the post infection clinical course. By a mean age of 29 months, 18 infants (38%) had been hospitalized a total of 30 times with acute respiratory distress and 27% of the infants were admitted during the first year of life. Respiratory syncytial virus accounted for 33% of hospitalizations in the first 12 months of life, and these children experienced a prolonged hospitalization (mean duration, 22 days). Forty-three percent of hospitalized infants required mechanical ventilation.

Hematopoietic stem cell transplant recipients and RSV infection. Respiratory syncytial virus infection in an immunocompromised host may be unsuspected when illness begins with mild upper respiratory tract symptoms. Without vigilance, the opportunity to initiate early therapy may be missed. Bronchoalveolar lavage is recommended for bone marrow transplant recipients with symptomatic respiratory disease if an etiology is not determined quickly from diagnostic samples obtained from the upper airway. Harrington et al[35] reported over 3 months, 31 cases of RSV infections among 199 transplant recipients, representing an attack rate of 16%. Twenty-three of the 31 (74%) patients had been inpatients for >7 days when infection was first identified, emphasizing the potential for nosocomial transmission, even in a carefully monitored setting. The remaining 8 patients had visited the outpatient department within one week of onset of upper respiratory tract infections. Eleven of 14 (79%) pre-engraftment patients and 7 (41%) of 17 post-engraftment patients developed RSV pneumonia. The results of studies in autologous as well as allogeneic bone marrow transplant recipients have demonstrated that infection with RSV is associated with prolonged hospitalization and mortality rates that may be as high as 60-80%, despite intervention with antiviral therapy. Preengraftment patients appear to develop lower respiratory tract disease at higher rates (70-80%) than post-engraftment recipients (25-40%).

Solid organ transplant recipients and RSV infection. Pohl et al[36] reviewed the course of 493 pediatric liver transplant recipients and identified RSV in 17 subjects. Median time to diagnosis was 24 days post transplantation, with a median patient age of 20 months. Thirteen of the 17 (76.5%) RSV cases were nosocomial, reemphasizing the importance of adherence to isolation guidelines. Five of 17 required intubation, and 2 died.

Immunodeficiency disorders and RSV infection. Deficits in cellular immunity associated with malignancy, chemotherapy and other immunodeficiencies result in more severe RSV disease than in a normal host. Hall et al[37] evaluated 47 RSV-infected children who were immunocompromised secondary to congenital immunodeficiency disease, chemotherapy or steroid therapy. In comparison with normal children or children treated with corticosteroids alone, these groups had a significantly increased use of the intensive care unit. Among all groups of immunocompromised children, RSV was shed for longer periods and in greater quantity than among RSV-infected children with an intact immune system. Crooks et al[38] evaluated respiratory disease in 73 infants and children with primary immunodeficiency disorders, including severe combined immunodeficiency and adenosine deaminase deficiency. Twenty-two of 73 (30%) developed symptoms of respiratory viral infections at the time of bone marrow transplantation, and 7 (32%) of these patients died of viral pneumonitis.

Human immunodeficiency virus (HIV) infection and RSV infection. Chandwani et al[39] followed 10 HIV-infected patients with RSV disease. Eight children were seropositive for HIV, and 2 were diagnosed with HIV at the time of their RSV infection. Two of the HIV-infected children with RSV disease died, although this pathogen was not recovered from lung tissue obtained at autopsy. Results of studies from Sub-Saharan Africa, where the prevalence of maternal HIV is >25% and where mother-to-infant rates of HIV transmission are high, demonstrate a risk for severe lower respiratory tract disease caused by RSV that extends beyond 6 months of age and a higher case fatality rate in HIV-infected children (who were not receiving antiretroviral therapy) relative to HIV-uninfected children.[40] In a study from South Africa, the estimated incidence for RSV-associated with severe lower respiratory tract illness in young, untreated HIV-infected children was at 1444 per 100,000 as compared to 309 per 100,000 in the HIV-uninfected population.[41]

Incubation period. The incubation period from exposure to first symptoms is approximately 4 days. The virus is excreted for variable periods, probably depending on severity of illness and immunologic status. Most infants with lower respiratory tract illness shed virus for 5-12 days after hospital admission. Excretion for 3 weeks and longer has been documented. Spread of infection occurs when large, infected droplets, either airborne or conveyed on hands, are inoculated in the nose or conjunctiva of a susceptible subject. Respiratory syncytial virus is probably introduced into most families by schoolchildren undergoing reinfection. Virus is usually spread from child to child on the hands of caregivers. Adults undergoing reinfection have also been implicated in spread of the virus.[10]

Clinical manifestations. The RSV infection in infants has 4 different clinical presentations. The most frequent presenting mode is acute bronchiolitis characterized by an obstruction of the bronchioles with air trapping. Rhinorrhea, cough, expiratory wheezing and respiratory distress[10] generally characterizes bronchiolitis, which is primarily seen in infants and children younger than 2 years of age. Cough may appear simultaneously but more often after an interval of 1-3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse rhonchi, fine rales or crackles, and wheezes. Abundant, clear rhinorrhea usually persists throughout the illness, with intermittent fever. Roentgenograms of the chest at this stage are frequently normal. If the illness progresses, cough and wheezing increase and air hunger ensues with increased respiratory rate, intercostal and subcostal retractions, and hyperexpansion of the chest. Signs of severe, life-threatening illness are central cyanosis, tachypnea of more than 70 breaths/minute, listlessness, and apneic spells. At this stage, the chest may be greatly hyperexpanded and almost silent to auscultation due to poor air exchange. Pleural effusion is rarely, if ever, seen. The second presentation of the illness may be more like pneumonia with the prodromal rhinorrhea and cough followed by dyspnea, poor feeding, and listlessness, with a minimum of wheezing and hyperexpansion. Although the clinical diagnosis is pneumonia, wheezing is often present intermittently and the chest roentgenogram may show air trapping. The third presentation of the illness in young infants, particularly those who were born prematurely, is periodic breathing and apneic spells, which could be distressing, even with relatively mild bronchiolitis. Finally, RSV infection may present as circulatory failure. Particularly in young infants admitted to intensive care unit (ICU), the occurrence of arrhythmia, myocarditis, and cardiogenic or septic shock has been reported.[42]

Pathogenesis. Bronchiolitis is characterized by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round cell infiltration and edema of the surrounding submucosa. These changes result in formation of mucous plugs obstructing bronchioles with consequent hyperinflation or collapse of the distal lung tissue. Infants are particularly apt to experience small airway obstruction because of the small size of the normal bronchioles. Although the precise contributions of antibody- and cell-mediated immunity in response to initial or recurrent RSV infections continue to be elucidated, information gained thus far is paving the way to research and development of effective anti-RSV vaccines.

Antibody-mediated immunity. During the first 2 months of life, passively acquired maternal immunoglobulins protect newborns against infection with RSV. However, the presence of maternal antibodies decreases gradually during the first 6 months of life, leaving most infants unprotected against RSV between 2 and 4 months of age.[43] Primary infection with RSV appears to induce weak serum antibody responses, especially in children <3 months of age, probably due to the presence of maternal antibodies. In children <6 months of age, the humoral antibody response is constituted primarily of mucosal immunoglobulin (IgA) in respiratory secretions rather than serum IgG.[44] Overall humoral responses are stronger if primary infection occurs after 6 months of age. These responses are also enhanced after each subsequent episode of reinfection throughout life. Immunoglobulin (IgM), IgA and IgG responses to RSV do not differ with the type of illness, namely upper versus lower respiratory tract disease.[45]

Humoral and secretory antibodies targeted at the fusion and attachment viral surface proteins are probably most important;[46] however, these antibodies offer limited only protection against reinfection.[47,48] Resistance to RSV reinfection has been shown to correlate better with serum antibody than with secretory antibody titers. However, increased serum IgG titers do not entirely guarantee that a person will be protected from acquiring a new RSV infection or that future disease will be mild.[44] These data suggest that there is an unknown component of the immune system that is equally important to serum antibody in preventing RSV infection or in restricting its spread to the lower respiratory tract.

Cell-mediated immunity. Epithelial cells initiate the inflammatory response to RSV by elaborating a wide variety of cytokines and chemokines that trigger further inflammatory responses. T cells produce proinflammatory mediators categorized as type 1 cytokines (Th1) or type 2 (Th2) cytokines. Type 1 cytokines cells secrete interleukin IL-1, tumor necrosis factor-alpha, IL-6, IL-8, macrophage-inflammatory protein (MIP)-1-alpha and regulated upon activation, normal T cell expressed and secreted (RANTES). Type 2 cytokines cells[3] produce IL-4, IL-5, IL-6 and IL-13. IL-4, IL-5, and MIP-1 promote IgE production and eosinophilia.[49] Release of these cytokines and chemokines appears to be at least partially responsible for airway inflammation and bronchial hyperresponsiveness, as well as upper respiratory symptoms.[50] Once these chemical mediators find their way into the airway, recruited cells prolong the inflammatory response with further cytokine/chemokine release that attracts and up-regulates other inflammatory cells. The release of these chemical substances may persist for months after clinical evidence of infection has disappeared. When there is an imbalance in Th1 and Th2 responses, disease severity is enhanced.[51,52] Some chemokines attract a broad array of cells, whereas others are cell-specific. Macrophage-inflammatory protein-1-alpha attracts and activates lymphocytes and eosinophils, as well as stimulates mediator release from basophils, particularly in atopic individuals.[53] Sheeran et al,[54,55] analyzed respiratory secretions from 28 infants with severe RSV disease (14 intubated, 14 nonintubated), compared with 7 controls with no respiratory disease, who were intubated for elective lower abdominal surgeries. The results showed that chemokine concentrations in the upper and lower respiratory tract secretions from RSV-infected children were significantly more elevated than controls in the first few days but then declined during the 5 days of the study period. In addition, chemokine concentrations correlated with RSV viral load in the nasopharyngeal secretions. Day 1 tracheal aspirate concentrations of RANTES and interleukin-8 showed a significant correlation with markers of disease severity (defined as days of intubation and total days of supplemental oxygen requirement). Garofalo et al[56] observed that nasopharyngeal concentrations of MIP-1-alpha, an attractant of eosinophils, and monocyte chemotactic protein-1 parallel severe forms of bronchiolitis. Chemokines may be responsible for causing the development of severe forms of RSV-related illness.[57-61] Once infection is established, the cellular immune response (including cytotoxic and helper T cells) promotes viral clearance.[62] Respiratory syncytial virus shedding generally stops within 21 days after infection in healthy infants and young children; in contrast children with cellular immunodeficiency can shed virus for several months.[63]

Neuroimmune mechanisms. Compromised epithelial integrity, the elaboration of local proinflammatory mediators and dysfunction of neural pathways may all influence airway responses to environmental stimuli.[64] Some investigators postulate that infection with RSV and similar viral pathogens can precipitate an imbalance in local cell-mediated immune responses.[65] Others theorize that infant bronchiolitis may result in alterations to neuronal pathways that influence smooth muscle tone and airway patency via the release of neurotransmitters.[64] A third group has proposed that combined neuroimmune interactions primed by the virus can both initiate and propagate a cascade of inflammatory events that determines recurrent cycles of mucosal edema, bronchial hyperreactivity and reversible airway obstruction.[66] In the airways, a dense network of sensory nerve fibers is strategically placed just below the epithelial surface so that any change in the bronchial environment may stimulate the release of the proinflammatory neuropeptide substance P. During RSV infection, stimulation of these nerves in rats caused a marked increase in airway vascular permeability in comparison to pathogen-free rats and resulted in an increase in overall inflammatory status. These changes are mediated by the high affinity receptor for substance P [neurokinin (NK) 1 receptor], the expression of which is greatly increased by RSV. This up-regulation presumably occurs at the gene expression level, as NK1 receptor mRNA levels increase substantially during RSV infection.[67] As a consequence stimulation of the sensory nerves by any airborne irritant has the potential of causing a new inflammatory cycle mediated by NK1 receptor-expressing T lymphocytes attracted into the airways and activated by substance P. This mechanism may establish important neuroimmune interactions, which undergo long-term dysregulation after RSV infection and predispose to airway inflammation and hyperreactivity.[68] Moreover, most recent studies show that RSV infection promotes a

large increase in the expression of nerve growth factor (NGF) and neurotrophin receptors.[69] Respiratory syncytial virus-induced release of NGF leads to short and long term changes in the distribution and reactivity of sensory nerves across the respiratory tract, participating to exaggerated inflammatory reactions during and after the infection. Nerve growth factor and its receptors may also amplify other immunoinflammatory and neuronal pathways contributing to airway inflammation and hyperreactivity.

The link between RSV, wheezing and asthma. Does RSV directly cause wheezing and airway hyperreactivity or is it just an early marker that signals that the child is at increased risk for developing chronic lung disease? Respiratory syncytial virus persists or in some way affects the immature respiratory and immune systems of the infant, predisposing the host to recurrent respiratory tract infections, bronchial hyperreactivity and long term pulmonary and immunologic sequelae (the consequential hypothesis). Alternatively susceptible infants may have preexisting diminished lung function and/or a genetic susceptibility to the development of lung disease (the common causal hypothesis).[70] Both explanations may be true. For children who experience RSV infection at a young age (≤3 years), there is an increased risk of wheezing and asthma that may persist for 8-13 years postinfection;[71] at which point past exposure to maternal cigarette smoking becomes a more important determinant of wheezing than RSV infection. Children who develop asthma at a relatively young age (7-9 years) after bronchiolitis in infancy also are more likely to be atopic. As such, atopic disease is another contributor to postbronchiolitic wheezing. In addition, children who had peripheral blood eosinophilia and eosinophilic cationic protein in blood at the time of RSV infection are also more likely to develop asthma at a young age.[72]

In the Swedish study, 47 children with confirmed RSV bronchiolitis in infancy were followed to determine the risk of bronchial obstructive disease and allergic sensitization at ages 1, 3 and 7.5 years. [73] Ninety-three age and gender-matched RSV-negative control children were also followed. The occurrence of "asthma" or "recurrent wheezing" episodes was determined by questionnaire, with "asthma" being defined as at least 3 episodes of bronchial obstruction verified by a physician. Cumulative and current prevalence of asthma as well as recurrent wheezing were significantly higher in the RSV group than in controls at age 7.5 years. Allergic sensitization was also significantly more prevalent in the RSV group than in the control group. A multivariate analysis of these observations identified RSV bronchiolitis as an independent risk factor for asthma and also as an important risk factor for any wheezing and for allergic sensitization. The most important risk factor for allergic sensitization was double parental history of atopy, followed by RSV bronchiolitis. Respiratory syncytial virus bronchiolitis appeared to be a more important risk factor for the development of asthma up to age 7.5 years than heredity for atopy/asthma, male gender or various environmental factors. Further in-vitro studies of 37 ex-bronchiolitic children from this same cohort have shown that peripheral blood mononuclear cells stimulated with RSV contain a significantly higher frequency of interleukin (IL)-4-producing T cells than 69 matched controls. The frequency of interferon-gamma (IFN-gamma)-producing T cells was the same for both groups. As a result of these observations, it has been suggested that RSV bronchiolitis in infancy may increase the risk of allergic sensitization through providing a local IL-4-rich environment in which aeroallergens are first encountered.

In the Nottingham study,[74] 61 index children admitted to the University Hospital in Nottingham during the 1979 to 1981 winter epidemics were evaluated with 47 children recruited from a previous 5.5-year assessment served as matched controls. The prevalence of wheezing among index children was more than 3 times that of the uninfected control group. Twenty (33%) of the index children and only 2 (3%) of the controls were receiving treatment with bronchodilators, and 7 of the index children were also on prophylactic antiasthma therapy. No statistically significant differences were observed in static lung volume measurements among index and control groups. However, measurements affected by airway obstruction showed a statistically significant reduction of >5% in forced expiratory volume (FEV)0,[75] and FEV1.0 as well as reductions in expiratory flow measurements of up to 15% in the index children versus the controls. According to a stepwise logistic regression model, a history of bronchiolitis was the only variable significantly related to wheezing, coughing or asthma diagnosis. In the Tucson Children's Respiratory Study,[75] a large cohort of children, from birth to 13 years of age was followed for the prevalence of recurrent wheezing and atopic sensitization. Children with a history of RSV infection were at increased risk of recurrent wheezing at the age of 6, but this risk had declined to insignificance by age 13. In the RSV-positive group FEV1 measured at 11 years of age was significantly diminished, yet reversible with the use of inhaled albuterol. Eosinophil counts in persistent wheezers remained elevated during the convalescent phase of respiratory infection, unlike those in the "nonwheezer" and transient wheezer groups. Persistent wheezers also tended to share certain characteristics of children at risk for asthma, including higher concentrations of serum IgE,

history of maternal asthma and higher incidence of atopic dermatitis. Recently, a new model emerged that could explain these nonpersistent wheezing phenotypes.[76] According to this model, asthma would be the result of convergence in the same individual of 2 parallel and relatively independent components. The immune component would be determined by an intrinsic imbalance between Th1 and Th2 mechanisms controlling the mucosal immune responses in the airways, favoring the latter, with the consequent predisposition to allergic inflammation and atopy. The other component would consist in a dysfunctional communication between epithelium and underlying mesenchymal structures, involving the aberrant release of and responsiveness to trophic factors, which determines the abnormal growth of smooth muscle, nerves, blood vessels and other structural components, namely remodeling of the airways.

Indicators of severe RSV disease. Measures of serious RSV infection include the rate and duration of hospitalization, ICU admission, oxygen requirement and mechanical ventilation. Mortality resulting from RSV infection is rare in developed countries, occurring in <0.1% of cases.[77] The highest case fatality rate of 3-5% is found among children who have chronic lung disease, CHD or immune deficiency.[78] Conversely, mortality caused by RSV infection appears to be common in developing countries, where mortality rates in infants and children with RSV bronchiolitis are similar to or higher than the rate found in chronically ill children in developed countries. Overall, the variations in morbidity resulting from RSV infection depend on the population demographics (namely infants versus elderly; high risk populations versus low risk populations), the setting of the study (hospital-based versus community-based cohort studies versus community-based cross-sectional studies), mode of sampling (nasal wash and nasopharyngeal aspirate (NPA) versus nasal swabs) and the method of detection of the virus (culture versus rapid testing), along with other factors.

Diagnosis. Bronchiolitis is a clinical diagnosis. The white cell count is normal or elevated, and the differential count may be normal with either a neutrophilic or mononuclear predominance.[10] Hypoxemia is frequent and tends to be more marked than anticipated on the basis of the clinical findings. When it is severe, it may be accompanied by hypercapnia and acidosis. The diagnostic dilemma of greatest importance is the question of possible bacterial or chlamydial involvement, because such presence dictates the possible use of antimicrobials. When bronchiolitis is clinically mild or when infiltrates are absent by roentgenogram, there is little likelihood of bacterial component. Chest radiographs of infants hospitalized with RSV bronchiolitis are normal in approximately 10% of cases; air trapping or hyperexpansion of the chest is evident in approximately 50%. Peribronchial thickening or interstitial pneumonia is seen in 50-80%. Segmental consolidation occurs in 10-25%. Consolidation without other signs or with pleural effusion is considered of bacterial origin until proved otherwise. Other signs suggesting bacterial pneumonia are elevation of the neutrophil count, depression of the white cell count in the presence of severe disease, ileus or other abdominal signs, pleuritic pain, high temperature, and circulatory collapse. In such instances, there is rarely any doubt about the need for antibiotics. Definitive diagnosis of RSV infection is based on the detection of virus or viral components in respiratory secretions. An aspirate of mucus or a nasopharyngeal wash from the child's posterior nasal cavity is the optimal specimen. A nasopharyngeal swab is also acceptable. A tracheal aspirate is unnecessary. The specimen should be placed on ice, taken directly to the laboratory, and processed for antigen 10.

Treatment. The American Academy of Pediatrics Committee on Infectious Diseases recommends supportive care as needed, including hydration, supplemental oxygen, and mechanical ventilation as the primary treatment modalities for bronchiolitis. Several other interventions designed to relieve airway obstruction, however, have been used. Those strategies have included mechanical removal of intraluminal debris, reduction of inflammation, relief of bronchospasm or use of different respirable gases such as helium to reduce airway resistance. Agents that have been used to achieve these goals include corticosteroids, bronchodilators, helium/oxygen (heliox) therapy and exogenous surfactant. Such therapies aim at attenuating the duration of disease, reducing morbidity and mortality and preventing or shortening hospitalization. However, there is no clear consensus on the routine use of these agents at present. Treatment of RSV should be individualized and careful assessment is essential.

Fluid replacement and supplemental oxygen. It is important to ensure that infants with RSV bronchiolitis are adequately hydrated. Fluid deficits occur when fever and tachypnea increase fluid demands, whereas dyspnea and tachypnea limit adequate intake. Administration of parenteral fluid is often necessary, because it is difficult for many infants to suckle and breathe simultaneously.[1,79] However, fluid administration should be carefully monitored to avoid fluid overload with subsequent pulmonary congestion. Infants with severe obstruction are also at risk to experience the syndrome of inappropriate secretion of antidiuretic hormone, and pulmonary congestion will be exacerbated by liberal fluid replacement. To avoid such complications, it has been suggested that

fluid deficits and ongoing losses be replaced at two-thirds maintenance levels. Infants with acute RSV infection requiring hospital care should be continuously monitored and receive supplemental oxygen to correct hypoxemia when present. Cardiorespiratory monitoring should include continuous pulse oximetry readings. Warmed, humidified oxygen administered with a nasal cannula, headbox or tent is appropriate for infants with oxygen saturation levels of <92% on room air. Nasal passages should be kept clear with saline drops and suction. Supplemental oxygen may be weaned when the pulse oximetry exceeds 92%. More intensive monitoring may be indicated in children at high risk for apnea. Intensive care and mechanical ventilation may be required for children who develop apnea or respiratory failure (defined as partial pressure of carbon dioxide >55 torr and partial pressure of oxygen <70 torr in an infant receiving 60% oxygen).

Corticosteroids. The use of systemic corticosteroids in bronchiolitis is based on the hypothesis that the anti-inflammatory action of these agents can reduce bronchiolar swelling, thereby relieving airway obstruction. The 2003 Red Book states: "In hospitalized infants with RSV bronchiolitis, corticosteroids are not effective and are not indicated." Studies examining the use of corticosteroids given by inhalation during the acute course of bronchiolitis have shown no decrease in the duration of symptoms or reduction in the number of episodes of wheezing after the acute episode of bronchiolitis.[80,81] Although corticosteroids are widely used, clinical studies have not shown clear evidence of efficacy in reducing symptoms or shortening hospitalizations.[82] Garrison et al[83] performed a meta-analysis of randomized, placebo-controlled trials of systemic corticosteroids and extracted data for length of stay, duration of symptoms and clinical scores for hospitalized infants with mild to moderate disease. In the pooled analysis, infants who received corticosteroids had a slight but statistically significant improvement in all measures. The length of stay and duration of symptoms were reduced by 0.43 day in patients, with mild to moderate disease, who received systemic corticosteroids. Secondary analyses showed that the greatest benefits were observed in patients who were receiving mechanical ventilation and those with higher symptom scores at study entry. The meta-analysis suggested that disease severity and timing of therapy might correlate with the benefits of corticosteroid therapy. Therefore it may be useful to target infants with severe disease when utilizing corticosteroid therapy. Schuh et al[84] recently demonstrated the benefit of early use of oral dexamethasone to infants with mild to moderate bronchiolitis in the emergency room. The results show fewer hospital admissions and more rapid improvement in clinical score compared with those infants who received placebo. Given current evidence, systemic corticosteroids do not seem to offer an overall benefit.

Bronchodilators. Randomized clinical trials of bronchodilators including oral, and inhaled beta-2-agonists, combined alpha- and beta-agonists and anticholinergics have yielded variable results.[85] Bronchodilators are effective in asthma, where increased smooth muscle tone is a prominent contributor to airway obstruction. Because not all children with bronchiolitis have bronchospasm and bronchial hyperreactivity, it is logical to expect that bronchodilators may not have efficacy across the population of patients with bronchiolitis.

Beta-2-agonists. Flores and Horwitz[86] found no evidence that beta-2-agonist use either improved oxygenation by a clinically significant amount or reduced admission rates from outpatient and emergency department settings in a meta-analysis that included 8 RCTs. In a Cochrane review, Kellner et al[87] examined 20 RCTs and found a statistically significant increase in the proportion of bronchodilator-treated infants who demonstrated an improvement in their clinical. However, bronchodilator recipients did not show improvement in measures of oxygenation; the difference favored the control population. The rate of hospitalization was not significantly reduced in bronchodilator recipients compared with controls.

Combined alpha- and beta-agonists. Wohl and Chernick[88] postulated that use of a combined alpha- and beta-adrenergic agent would improve lung function in infants with bronchiolitis because the alpha-adrenergic component would diminish airway mucosal edema, while the beta-adrenergic would cause bronchodilatation. King et al[89] reviewed 8 RCTs where nebulized epinephrine has been compared with placebo and nebulized beta-2-agonist bronchodilators, salbutamol and albuterol. The total number of children studied in these trials was 660. Few results favoring nebulized epinephrine emerged, and most outcomes reported were short term. Of 5 trials that examined duration of hospitalization, 2 noted either shorter hospitalization or fewer admissions in the epinephrine versus salbutamol group. Five studies commented on changes in clinical scores measured at various times. Three studies reported better clinical scores immediately after initial treatment compared with placebo and salbutamol but data at 24 and 36 hours did not see a persistent improvement. Aside from some transient improvements in clinical scores and related measures, little evidence was found to suggest that epinephrine is an effective treatment for bronchiolitis.

Anticholinergic agents. Another class of bronchodilators, anticholinergic agents, has been assessed alone or in combination with

beta-2-agonists in infants with bronchiolitis to date anticholinergics have not been shown to be effective in altering duration of symptoms or lung mechanics in infants with bronchiolitis.[90]

Combination therapy. Use of a corticosteroid plus a bronchodilator may offer more benefit than either agent alone. In a double blind trial, Tal et al[91] compared intramuscular dexamethasone or placebo (double blind) and salbutamol (oral and inhaled), or none (open), in all 4 possible combinations in infants hospitalized with acute wheezing. The results showed that average daily improvements in clinical score and hospital length of stay were comparable among infants treated with placebo, salbutamol alone and dexamethasone alone. However, there was a significant shortening of duration of hospitalization in infants receiving the combination of salbutamol and dexamethasone versus other treatments ($p<0.01$). In addition, response was observed within 24 hours in the combination therapy arm. Also, worsening did not occur among patients who received the combined salbutamol-dexamethasone treatment. The authors speculated that corticosteroids might potentiate beta-adrenergic responsiveness.

Mechanical ventilation. The proportion of infants requiring controlled mechanical ventilatory support for bronchiolitis is variable. In one American study, 1.7% of infants <1 year of age were intubated and/or received ventilatory support.[92] A Canadian multicenter study[93,94] included 689 infants hospitalized for lower tract RSV infection during the 1993 epidemics. In this study, mean age was 9 months, 16.1% of the infants were admitted to ICU, and 9.1% needed mechanical ventilatory support. There was no difference between infants with underlying disorders and premature infants or infants aged <6 weeks. However, infants without any risk factor had significantly lower ICU admission and intubation rates. The determined risk factors included: apnea or respiratory arrest, hypoxia defined as a pulse oximetry recording of <90% in room air, and the presence of infiltrates on chest x-ray. In this 1993 Canadian study, the mortality rate was 0% for infants without a preexisting cardiac disease and 5.4% for those with a preexisting cardiac disease. The mortality rate was 1% for infants <6 weeks of age, 3.4% for infants with a gestational age of <37 weeks, 4.8% for immunocompromised infants, and 5.1% for those with a chronic lung disorder. Large international variation in the hospital management of RSV infection was documented in a retrospective multicenter study including 1563 patients from 41 children's hospitals in Europe, the United States, and Australia;[95] 33.3% were chronically ill or prematurely born infants, and the overall mortality rate was 0.5%. The median ICU admission rate was 8.5%. The proportion of children receiving mechanical ventilatory support was 2.2%. In previously healthy infants requiring controlled mechanical ventilatory support, the mortality rate is estimated to be <1%; whereas in infants with preexisting respiratory or cardiac disorders, it is 3.5%.[96]

Conventional mechanical ventilatory support. There is no consensus on the optimal ventilation strategy for infants with bronchiolitis.[97] No study has shown the superiority of assisted or controlled ventilation with pressure or volume mode.[98] Given the low mortality and morbidity associated with controlled mechanical ventilatory support in the treatment of RSV bronchiolitis, it is difficult to demonstrate the advantage of one particular mode over another. Optimal settings need to be refined to avoid secondary damage by barotrauma and volutrauma. Low respiratory rates should be used to avoid hyperinflation when bronchiolitis is present. High mean airway pressure with high rates may be necessary to improve oxygenation when the alveolar injury prevails. Commonly applied settings for controlled mechanical ventilatory support include a tidal volume (VT) of ≤ 10 mL/kg. Indeed, targeting a VT of 6 mL/kg probably reflects the most common current approach used in the setting of significant parenchymal lung disease.[99] Permissive hypercapnia has been studied retrospectively in 2 reports. Twenty-nine out of 68 patients who received ventilatory support and for whom hypercapnia was tolerated had significantly less barotrauma, shorter duration of ventilatory support and hospital stay, and reduced costs whereas mortality rates were similar.[100] In another report where hypercapnia was tolerated in 28 out of 47 infants, no difference was found for both the same outcomes listed above and for the use of neuromuscular blockade.[101] Generally, moderate hypercapnia is accepted if pH remains >7.25. The use of positive end-expiratory pressure (PEEP) in bronchiolitis is debated and surprisingly cannot be recommended based on controlled investigation.[102] Nevertheless, clinicians routinely use PEEP during controlled mechanical ventilatory support of infants with RSV. Its use is helpful when a reduction of intrinsic PEEP can be evidenced.[103] The use of PEEP is particularly indicated when the alveolar component of RSV infection prevails leading to acute respiratory distress syndrome.[104] Air leak complications (pneumothorax, pneumomediastinum, subcutaneous emphysema, and pneumopericardium) are uncommon if the ventilation strategy is aimed at reducing barotrauma and volutrauma. The Groupe Francophone de Réanimation Pédiatrique reported that 5% of infants with RSV infection and receiving ventilatory support had barotrauma.[105] Briassoulis et al[32] did not observe air leaks in eight infants with

bronchiolitis and receiving ventilatory support with a VT of 7-10 mL/kg, rapid respiratory frequency, and a maximum peak inspiratory pressure of 28 cm H_2O.

Physiotherapy. No evidence for the effectiveness of physiotherapy in acute bronchiolitis was reported in a review of physiotherapy in children receiving mechanical ventilatory support.[106] Furthermore, irrespective of the indications for controlled mechanical ventilatory support, chest physiotherapy was associated with more extensive atelectasis, a longer stay in ICU, increased episodes of gastroesophageal reflux, and an increased intracranial pressure. Therefore, this treatment should be considered as a potentially stressing intervention procedure and should be performed only with careful cardiorespiratory monitoring.

Ribavirin. Ribavirin[107] is a nucleoside analog approved for treatment of RSV. Ribavirin has a broad spectrum of activity in-vitro against measles virus, RSV, influenza A and B, parainfluenza, adenovirus, hepatitis viruses and other viruses. It is a virustatic agent that inhibits viral replication during the active replication phase. However, the exact mechanism of action of ribavirin in-vivo remains unknown. It is thought that ribavirin may also favor a type I response in active T cells and reduce RSV-specific IgE loads. One of the earlier trials was a prospective, double blind, multicenter study by Groothuis et al[108] who reported that early administration of ribavirin (≤72 hours after symptom onset) among 20 high risk children with underlying lung disease and/or pulmonary hypertension was associated with a reduction in morbidity, compared with 27 placebo recipients. After 3 days of therapy, ribavirin produced a greater rate of improvement in analog scores (p=0.001), lower oxygen requirements (p=0.01) and higher oxygen saturation (p=0.01) versus placebo. Identifying low risk infants (<72 hours) in the course of RSV illness may be a challenge that may limit broader application of these findings. Conversely in a subset analysis of 750 children with community-acquired RSV lower respiratory tract infection, who were prospectively enrolled in the 1993 to 1994 RSV database, the Pediatric Investigators Collaborative Network on Infections in Canada[109] observed no significant benefit of ribavirin therapy on outcomes in the subgroups of premature infants, infants with CHD, chronic lung disease or early hypoxia. Although this study may represent the "true life" experience with ribavirin, several limitations need to be considered: (1) patients treated with ribavirin were sicker than those not treated; (2) patients were not randomized for ribavirin treatment or lack of it; and (3) instead of being treated early in the course of RSV illness, some patients were started on ribavirin therapy as late as the seventh day of hospitalization (in addition to the number of days of symptoms before admission). This study simply reemphasizes the importance of early treatment, clearly suggesting no benefit during acute RSV illness if antivirals are used late in its course. The use of ribavirin is further constrained by its high cost and possible risk to health care personnel who administer it. A systematic review of 8 RCTs of ribavirin therapy published by Randolph and Wang[110] in 1996 found that ribavirin use does not significantly affect mortality, lower the likelihood of respiratory compromise, or shorten hospitalization. However, statistical power is insufficient to rule out an effect. Delivery of ribavirin necessitates special precautions and a particular aerosol device. A recent randomized controlled prospective double blind trial did not show any benefit in healthy infants with RSV bronchiolitis who had previously received ventilatory support.[111] The 20 patients treated with ribavirin had similar duration of ventilatory support, oxygen therapy, and hospital stay when compared with the 21 patients treated with saline. There were no air-leak complications or deaths. This study confirmed previous data from a similar trial that included 41 infants (24 with nucleoside analog approved for treatment of RSV cardiopulmonary disease).[112]

Helium. Helium is a biologically inert gas of low molecular weight that is one-eighth the density of nitrogen. When blended with oxygen, the resulting gas mixture has a marked reduction in density compared with air (specifically, it has a 3-fold reduction when blended with 21% oxygen). This reduction of density will have 2 consequences, depending on the flow conditions within the airways. First, the lower the density, the lower the Reynolds number and the more likely it is that laminar conditions will prevail. Consequently, the flow for a given driving pressure will be higher. Second, in turbulent conditions, the flow rate is inversely related to density, meaning that for a given driving pressure, flow will again be higher if density is lower. In summary, the use of helium and oxygen (heliox) in the setting of obstructive airway disease is equivalent to decreasing airway resistance to flow and ultimately the work of breathing. The use of a mixture of heliox has been considered to decrease the need for intubation and controlled mechanical ventilatory support.[113] Hollman et al[114] described the effect of heliox in 18 infants (mean age 2.5 months) who were admitted to ICU for RSV bronchiolitis. Eleven had no preexisting disorder, and 5 had CHD. Heliox was administered through a facemask with a reservoir. After 20 minutes, there was a reduction of the clinical score from 4.25 to 3.02 (p<0.01) and an increase in arterial oxygen saturation of 1.8% (p<0.02). One patient did not respond sufficiently and needed controlled mechanical ventilatory

support. One limitation of this study was the fact that only 9 patients received only heliox after the initial 20 minutes study period. Six infants were also treated with continuos positive airway pressure because of persisting severe respiratory distress.

In conclusion, RSV infection occurs in predictable, annual outbreaks and is a major cause of both upper and lower respiratory tract disease in children and adults. Most infants with bronchiolitis who do not have underlying conditions can be managed successfully as outpatients. Nonetheless, hospitalization rates for lower respiratory tract disease in many young children appear to be increasing. As more children and adults become immunocompromised as a result of the increasing use of organ transplantation and chemotherapeutic agents, greater attention is likely to be focused on the importance of RSV as an opportunistic pathogen.

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