BRONCHIOLITIS IN THE PEDIATRIC POPULATION

By

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To the Faculty of Washington State University:

The members of the Committee appointed to examine the clinical project of ELYSE SUZANNE LEVITCH find it satisfactory and recommend that it be accepted.

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Abstract

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December 1999

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Predictable widespread outbreaks of illness are caused by bronchiolitis each year. Peak incidence is between two and six months of age. Severity of disease and outcome are highly variable. Significant morbidity is associated with persistent airway derangement. This manuscript examines infant anatomy, known pathophysiology, differential diagnosis, treatment and prevention. Further research into host inflammatory response to viral antigens is necessary to determine optimum treatment and prevent pulmonary morbidity.
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BRONCHIOITIS IN THE PEDIATRIC POPULATION

By

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Abstract

Predictable widespread outbreaks of illness are caused by bronchiolitis each year. Peak incidence is between two and six months of age. Severity of disease and outcome are highly variable. Significant morbidity is associated with persistent airway derangement. This manuscript examines infant pulmonary anatomy, known pathophysiology, differential diagnoses, treatment and prevention. Further research into host inflammatory response to viral antigens is necessary to determine optimum treatment and prevent pulmonary morbidity.
Introduction

Acute bronchiolitis is a serious lower respiratory tract infection. Manifested during the first two years of life, it is the most common severe lower respiratory tract infection (Hollman et al., 1998). Bronchiolitis can be caused by a myriad of pathogens, with viral entities causing the overwhelming majority. Respiratory syncytial virus type A and B are by far the most common pathogens, causing up to 50% of the reported cases (Welliver, 1998).

Predictable, widespread outbreaks of illness are caused by bronchiolitis each year (Hall, 1999). Severity of disease and outcome are highly variable. The diagnosis of bronchiolitis covers a broad spectrum of clinical presentation from mild lower respiratory symptoms to respiratory failure and occasionally death (Lemen, 1995). The intensity and magnitude of the pathogen along with the host response determines the severity of the disease (Domachowske & Rosenberg, 1999). The highest morbidity and mortality are seen in children with underlying diseases such as congenital heart disease, chronic lung disease, and immunodeficiency. Severe disease is also seen in infants less than six weeks of age with no underlying problem (Stretton, Ajizian, Mitchell, & Newth, 1992; Wang, Law, & Stephens, 1995).

Bronchiolitis is characterized by obstruction of small airways, which represents 50% of total airway resistance in this age group. Pathologic alterations of the small airways results in increased total pulmonary resistance. Consequently, total work of breathing is increased an average of six-fold in children with bronchiolitis (Hollman et al., 1998).
Significant morbidity is associated with persistent airway derangement caused by bronchiolitis. Bronchiolitis is the most important risk factor associated with continuing and future abnormal pulmonary function (McBride, 1999; Droste, Wieringa, Weyler, Nelen, Van Bever, & Vermeire, 1999). Studies suggest that up to 75% of children with viral bronchiolitis suffer recurrent episodes of coughing, wheezing and reactive airway disease (Fox, Everard, Marsh, & Milner, 1999). Children with a history of bronchiolitis early in life have a significant risk of developing atopy and asthma with obstructive symptoms (Sigurs, Bjarnason, Sigurbergsson, Kjellman, & Bjorksten, 1995). The pathophysiology of post bronchiolitic wheezing and poor pulmonary function remains unclear and difficult to prevent (Riehter & Seddon, 1998). The possibilities include increased airway reactivity, residual inflammation, and premorbid genetically small airway diameter (Hiatt, 1997).

Americans spend an enormous amount of health care dollars on children with bronchiolitis. The Institute of Medicine (1985) estimates annual costs of children hospitalized with this diagnosis are over three hundred million dollars, in the United States alone. The economic burden is even greater if outpatient visits, prolonged therapy, indirect costs to the family, and patients with underlying conditions are included. Direct and indirect costs are difficult to access (Hall, 1999). Analysis of preventive therapy and treatment modalities is essential to reduce suffering, morbidity and health care expenditures.

History

Bronchiolitis has been recognized in the medical literature for only a brief period of time. The term “capillary bronchitis” appeared in text in the early twentieth century.
Capillary bronchitis was used to describe an inflammatory illness of the smallest alveoli, but it was noted that this clinical condition could not be distinguished from pneumonia, and it was doubtful that the entity ever occurred separately. Holt’s Diseases of Infancy and Childhood, eleventh edition (1940), briefly discusses capillary bronchitis under the heading of pneumococcal pneumonia. Hubble and Osborn, in 1941, presented the first clinical description of epidemic bronchiolitis involving 50 hospitalized children. Pratt, Nelson, and Smith, 1944-45, published excellent antidotal clinical papers. Acute bronchiolitis was first listed under a separate heading in the Textbook of Pediatrics, sixth edition 1954, but even then it was associated with interstitial pneumonia (Welliver, 1998).

Chimps coryza agent, first isolated during a nosocomial outbreak of viral infection in a colony of fourteen chimps in 1956, was rechristened respiratory syncytial virus and later found to be the primary etiologic agent of bronchiolitis (Hussell & Openshaw, 1999). Other viral pathogens were isolated as the etiologic agents of acute bronchiolitis in the late 1950’s and early 1960’s.

The last 40 years has seen ongoing testing to try to determine the best treatment algorithm to reduce disease presence, severity of symptoms, morbidity, and health care burden. Field trials of formalin killed vaccine in the late 1960’s, induced enhancement of immunopathogenesis of disease. This dismal failure of vaccine has led to a greater understanding of the immunobiology of bronchiolitis (Domachowske & Rosenberg, 1999).
Anatomy

Reviewing normal infant anatomy is useful to understand the pathophysiology of bronchiolitis. Pulmonary development is incomplete at birth, it will continue to mature until approximately the eighth year of life. Newborn lungs contain 40 to 50 million alveoli, compared to 300 million present in the adult lung. Airway resistance in the infant is increased due to the proportionately small airway diameter relative to their mass (Schumann, 2000). Lack of elastic recoil predisposes the infant’s small airways to early closure (Mamlock, 1997). Compliance of the infants’ chest wall is increased, due to limited cartilage support (Boyer, 1999) and muscle mass (Schumann, 2000). Increased airway resistance, chest wall compliance, and lack of elastic recoil combine to make respiration more difficult.

Terminal respiratory tract differences also make ventilation more difficult. Alveolar membranes are thicker and have fewer capillaries in the child which makes gas exchange more tenuous (Schumann, 2000). Infants have an increased dead space to tidal volume ratio, forcing the infant to expend energy moving air that does not reach the alveoli for ventilation (Helfaer, Nichols, & Rogers, 1996). Young children also have less collateral ventilation due to lung immaturity. Pores of Kohn, which are interalveolar connections, are relatively non-existent. Immature lungs also have a relative deficiency of Canals of Lambert, which are redundant broncho-alveolar connections (Mamlock, 1997). Lack of collateral pathways such as the Pores of Kohn and Canals of Lambert restrict the infant and young child’s ability to compensate for terminal bronchiolar or alveolar blockage and make them more susceptible to obstruction and atelectasis (Evans, Kramer, & Kravitz, 1998; Welliver, 1999).
Infants also have an increased ratio of goblet cells, which are mucus secreting glands, that when stimulated can potentially produce a detrimental overabundance of mucus. Stimulation in the form of inflammation allows mucus to accumulate and occlude the lumen of small airways (Reed, 1997).

All of these anatomic pulmonary immaturities can predispose the infant to ventilation-perfusion mismatching, hypoxemia, hypercarbia, and respiratory failure.

**Pathophysiology**

Bronchiolitis is primarily an obstructive disease of the terminal bronchioles in infants, but fluid accumulation, hyperinflation, atelectasis and disruption of surfactant (Schwartz, 1995) indirectly affect larger airways and the alveoli (Jeng & Lemen, 1997). Pathologic findings of bronchiolitis are similar whether the etiologic agent is respiratory syncytial virus, parainfluenza virus, influenza virus, or adenovirus (Domchowske & Rosenberg, 1999).

Epithelial necrosis, destruction of the ciliated layer, sloughing of the airway epithelium (Wang et al., 1998), edema of the submucosa and adventitia, increased mucus production, smooth muscle constriction (Jeng & Lemen, 1997), and massive infiltration of the peribronchial tissues of the airway by polymorphonuclear cells (Jaovisidha, Peeples, Brees, Carpenter, & Moy, 1999) and mononuclear cells (Hanson & Shearer, 1999) are characteristic of bronchiolitis. The diameter of the small airway's lumen is reduced due to edema and smooth muscle constriction. Sloughed epithelial cellular debris, fibrin and mucus plugs fill the lumen, causing partial to complete obstruction of the small airways (Schweich, 1994). Loss of the ciliated epithelium prevents cellular debris and mucus from being mobilized and eliminated from the area causing air
trapping, hyperinflation, and atelectasis (Olszewska-Pazdrak et al., 1998). Obstruction of terminal bronchioles impedes airflow and gas exchange. Work of breathing and oxygen consumption are increased (Rakshi & Couriel, 1994). A ventilation-perfusion mismatch occurs and the infant becomes hypoxemic.

Respiratory syncytial virus, in addition, induces fusing of the membranes of adjacent epithelial cells which results in the formation of giant cells with multiple nuclei called syncytia (Reed, 1997), hence its name. These cells are incapable of functioning to clear the airways of debris and further hinder the infant’s pulmonary ventilation.

Host response when invaded by a viral pathogen is multifactorial. Initial immune response includes innate immunity using phagocytosis and activated natural killer lymphocytes (Guyton, 1991). Acquired immunity optimizes the production of humoral virus neutralizing antibodies and thymus derived lymphocyte specific immunity. T lymphocytes infiltrate the airway and play a critical role in the termination of viral replication. Humoral and cell mediated immunity are critical to the eradication of bronchiolitic viral infection (Domachowske & Rosenberg, 1999).

Abundant evidence indicates that immunologic mechanisms play a direct role in inciting the pathophysiologic changes seen in the lower airways with bronchiolitis (Helfaer et al., 1996). A fine balance exists between the protective and disease producing effects of thymus derived lymphocyte cells (Domchowski & Rosenberg, 1999). T cells with the CD4 marker are called helper cells. Recognition of antigens and secretion of lymphokines are CD4s’ primary roles. T cells with the CD8 marker are suppressor and cytotoxic cells. Suppressor cells keep the helper cells and humoral cells in check, and regulate immunoglobulin E production (Welliver, 1998). Cytotoxic cells
locate and lyse abnormal or invading cells. Effective immune function is regulated by the balance of helper, cytotoxic, and suppressor cells (Peterson, Symes, & Springer, 2000). Combined activity of CD4 and CD8 lymphocytes is necessary for complete antiviral activity (Domachowske & Rosenberg).

Viral disease activates CD4 cells to secrete lymphokines, which are proinflammatory mediators. The activated CD4 cells react initially with a T helper type 1 expression pattern, secreting interferon gamma, and interleukin 2. Interferon gamma inhibits viral replication, promotes antigen expression, and activates macrophages. Interleukin 2 promotes the growth and maturation of T cells (Peterson et al., 2000). T helper type 2 phenotype secretes interleukin 4 and 5 which promote humoral immune responses and are involved in switching humoral cells to immunoglobulin E production. These lymphokines are also capable of activating mast cells, basophils and eosinophils, which can lead to the presence of chemical mediators in the airway. Mediators such as leukotriene C4, histamine, tryptase, and kinins cause hyper-responsiveness, bronchiolar mucosal and submucosal inflammation, which can contribute considerably to illness (Welliver, 1999). Balance between T helper type 1 and 2 cytokine production is necessary to prevent recurrent wheezing after viral bronchiolitis (Renzi et al., 1999).

CD8 T lymphocytes are capable of clearing viral infection and may induce an enhanced inflammatory response. CD8 T lymphocytes accelerate clearance of the virus from persistently infected hosts. Unfortunately, CD8 cells are also capable of causing acute and sometimes fatal pulmonary damage under experimental conditions using mice with viral bronchiolitis (Domachowski & Rosenberg, 1999). Failure to control and
terminate the post-injury repair processes is linked to chronic inflammation, remodeling, and pathophysiological dysfunction of the airways.

Excessive cell mediated immune response and pulmonary damage may be a function of a relative deficiency of T lymphocyte suppressor cells. Immunoglobulin E levels correlates inversely with those of CD8 cells. T suppressor cells have a role in attenuating immune responses and IgE production. Levels of IgE are high in infants with bronchiolitis and correlate with the degree of hypoxemia (Domachowski & Rosenberg, 1999). Abnormal T cell regulation is seen in bronchiolitic infection which may explain the unrestrained production of immunoglobulin E (Lugo & Nahata, 1993). One mechanism postulated for bronchospasm and inflammation is an interaction between virally infected epithelial cells and specific IgE that leads to histamine release (Boyer, 1999). This non-balanced response may continue for several weeks after viral infection (Long, 1999; Hanson & Shearer, 1999).

Viral infections may provoke immunopathogenesis and wheezing by triggering enhanced inflammatory responses (Welliver, 1999). Polymorphonuclear cells have been shown to significantly augment viral infection induced damage and detachment of epithelial cells in vitro (Wang et al., 1998), which predisposes airways to hyperreactivity. Respiratory epithelial cells normally produce a number of substances that modulate vascular permeability and airway tone (Hiatt, 1997). Damage to these cells makes edema and bronchoconstriction more likely. Human epithelial cells upregulate many leukocyte chemoattractants in response to bronchiolitis (Harrison, Bonville, Rosenberg, & Domachowske, 1999). Observations that bronchiolitis infected epithelial cells secrete chemokines to attract leukocytes supports the hypothesis that leukocytes participate in the
immunopathogenesis of bronchiolitis. Leukocytes in the lungs help blunt viral replication, but overexcitement exacerbates the immunopathologic process (Domachowske & Rosenberg, 1999). Further studies are required to completely understand this mechanism (Jaovisidha et al., 1999).

Evidence exists that post bronchiolitic chronic airway disease is not singularly determined by the intensity or duration of the initial injury or genetic predisposition (Sorkness, Castleman, Kumar, Kaplan, & Lemanske, 1999). Host cells probably play an important role in the pathogenesis of viral bronchiolitis. Induction of inflammatory responses may be important in the eradication of viral infection, but research also suggests that exaggerated lymphocyte and polymorphonuclear response may play a role in the pathogenesis of viral induced chronic pulmonary derangement (Welliver, 1999). Airway inflammation with bronchiolitis is a multicellular process involving helper, cytotoxic and suppressor T lymphocytes, as well as polymorphonuclear cells.

Incidence

Bronchiolitis is the most common lower respiratory tract infection in infancy, affecting 11 to 12% of children in their first year of life (Flores & Horwitz, 1997; Welliver, 1998), and 6% in their second year (Halfaer et al., 1996). Three million children are infected annually (Long, 1999). Up to three percent of all infants require hospitalization during winter epidemics. In the United States approximately 91,000 infants are hospitalized yearly (Hall, 1999). Otherwise healthy infants who are hospitalized with respiratory syncytial virus bronchiolitis spend an average of five days confined (Wang et al., 1996), however children with underlying medical conditions may be hospitalized fifteen days or longer (McMillian, Tristram, & Weiner, 1988). One tenth
of hospitalized children will be admitted to in the Pediatric Intensive Care Unit, and 50% of children in the Pediatric Intensive Care Unit will require some form of assisted ventilation. The mortality rate of hospitalized children varies yearly between one and five percent depending on the presence or absence of various risk factors and underlying medical conditions (Piedra, 1997). According to the 1997 Morbidity and Mortality Weekly Report (MMWR), approximately 4,500 deaths are attributed to bronchiolitis in the United States annually.

**Epidemiology**

Bronchiolitis occurs in all geographic areas. Outbreaks are abrupt, predictable, and highly seasonal with peak activity during the winter months. In temperate climates yearly outbreaks occur between November and May usually peaking in January and February. The duration of outbreaks varies from year to year, but averages twenty-two weeks (MMWR, 1997). Virtually no bronchiolitis is seen between August and October (Welliver, 1998).

Bronchiolitis is primarily a disease of infancy. Highest rates of infection, severe disease manifestation, and mortality are seen between two and six months (Long, 1999), but it can be seen in children up to two years of age (Lehmen, 1995). Mean age of infants hospitalized is three months (Hall, 1999). More than 80% of cases occur during the first year of life (Welliver, 1998). Fifty percent of children will be reinfected in subsequent outbreaks (Long, 1999).

Lower respiratory tract infections, especially bronchiolitis, have a positive correlation to certain risk factors. Important risk factors for bronchiolitis include
exposure to environmental smoke, birth order, birth month, and family history of atopy or asthma. See Table 1.

Exposure of infants to environmental tobacco smoke is an important risk factor for bronchiolitis. Maternal smoking increases the risk of developing small airways in the unborn child and subsequent wheezing (Hanrahan et al., 1992). Smoking within the infant’s household increases the frequency of bronchiolitis by thirty percent, especially during the first two years of life (Bar-on & Zanga, 1996; Dybing & Sanner, 1999). Parental smoking provides a causal relationship between passive smoking and bronchiolitis in infants requiring admission to the hospital (Reese, James, Landau, & LeSouef, 1992).

Birth order is an important factor when considering bronchiolitis. Infants born into families with older siblings are more likely to contract bronchiolitis (Panitch, Callahan & Schidlow, 1993). Older children usually represent the index case and infants are secondarily infected (Reed, 1997). Older siblings are less likely to have clinically severe disease, and are most likely to introduce the virus to the infant (Lugo & Nahata, 1993).

Birth month also plays a role in the risk of bronchiolitis. Infants that are born during the months of mid to late year develop bronchiolitis more frequently (Panitch et al., 1993; Moreno & Donadeu, 1999). It is hypothesized that these infants reach their immunological nadir during the peak of viral activity, which makes them more susceptible to lower respiratory illness.

Family history of atopy or asthma is a significant risk factors for developing bronchiolitis (Moreno & Donadeu, 1999). Up to 60% of infants born to atopic parents
develop wheezing in the first year of life (Mamlock, 1997). Factors that predispose infants to wheeze may also increase the risk of viral infections becoming lower respiratory tract infections (Gold et al., 1999). Pediatric pulmonologists hypothesize that asthmatics have congenitally smaller airways, which predisposes them to wheezing. Small airways might be genetically passed to an offspring, which increases their risk of bronchiolitis (Welliver, 1998).

Certain underlying conditions predispose an infant to more complicated bronchiolitic disease. Substantial morbidity and mortality appears to be associated with these infants (Englund, Piedra, & Whimbey, 1997). The most severe infections occur in children with chronic pulmonary, cardiac, immunodeficiency (Hall, 1999), or a gestational age less than thirty-six weeks (O'Shea, Sevick & Givner, 1998). Apnea, respiratory failure and death are greater risk factors in this population (Piedra, 1997). See Table 2.

Chronic lung pathology or congenital heart defects cause predictably severe disease. Bronchopulmonary dysplasia, cystic fibrosis, persistent pulmonary hypertension and complicated or cyanotic heart disease require careful monitoring. Infants may be asymptomatic until they develop bronchiolitis, then rapidly deteriorate (Long, 1999). Thirty percent of children with underlying cardiopulmonary conditions require admission to the pediatric intensive care unit. Fifty percent of children in the intensive care unit require ventilatory assistance (Fixler, 1996).

Immunocompromized infants have a greatly increased risk of severe infection (Piedra, 1997). Prolonged viral shedding from the respiratory tract is observed in immunocompromised individuals suggesting that intact cell mediated immunity is critical
in the irradiation of viral infection. Both humoral and cellular immunity are necessary to successfully defend the body against viral bronchiolitis (Domachowske & Rosenberg, 1999).

**Etiology**

Respiratory syncytial virus is the most important lower respiratory tract pathogen of early life (Long, 1999), the major cause of bronchiolitis in infancy and virtually the only etiologic consideration when the disease is epidemic (Welliver, 1998). During periods of epidemic bronchiolitis, over 80% of the cases are due to respiratory syncytial virus. Nonepidemic periods reveal that respiratory syncytial virus is causal in up to 50% of cases (Long, 1999). See Table 3.

Respiratory syncytial virus is a group of negatively stranded RNA viruses from the Paramyxoviridae family, genus of pneumoviruses (McIntosh, 1996). Characteristic syncytial cell formation describes the multinucleated nonfunctional cells that give the virus its' name. Respiratory syncytial virus consists of two major serotypes labeled A and B, each with multiple genotypes. Groups differ primarily in the largest surface glycoprotein, the G protein. Due to the differences in viral structure, acquired immunity does not provide complete protection from subsequent infection (Long, 1999).

Parainfluenza is the second most common etiology of bronchiolitis. Resembling respiratory syncytial virus, parainfluenza are large RNA viruses belonging to the Paramyxovirus group. Types one and three are the most common pathogens in humans (Wright, 1996; Long, 1999).

Bronchiolitis may also be caused by rhinovirus, adenovirus types 3, 7, and 21, and influenza A and B (Halfaer et al., 1996). Mycoplasma pneumoniae and Chlamydia
trachomatis have also been identified in a few cases of bronchiolitis (Carballal, Mahoney & Videla, 1992).

**Clinical Presentation**

Bronchiolitis is a clinical diagnosis. Diagnosis is made by history, clinical presentation, age of the child, season of the year (Schweich, 1994), and viral prevalence in the community (Schwartz, 1995). History typically reveals an initial exposure of an infant to a sibling or an older child with mild upper respiratory symptoms during the winter months (Welliver, 1998). See Table 4. After incubation of three to seven days, with an average of four (Schwartz), a prodrome of upper respiratory symptoms heralds viral replication in the epithelium of the nasal pharynx (Domachowske & Rosenberg, 1999). Preliminary symptoms of upper respiratory infection include copious serous rhinorrhea, low-grade fever, and cough. Nasal congestion with tenacious secretions, progressive cough and upper airway obstruction dominates the clinical picture (Welliver, 1998).

Apnea may be the initial sign of disease in the infant less than two months. Viral bronchiolitis presents in 20-25% of infants in this manner (Bar-on & Zanga, 1996). Infants at greatest risk for apnea are less than 44 weeks conceptual age or prematurely born with a history of apnea of prematurity (Hall, 1999). Recognition of this symptom quickly routes the infant to the hospital. Monitoring for continued ventilation disturbances is essential (Larsen, Accurso, Deterding, Halbower, & White, 1997).

Viral spread to the lower respiratory tract is presumed to be by direct extension along the respiratory epithelium. Possibly, aspiration of viral laden nasopharyngeal
secretions or invasion of macrophages by the virus and subsequent migration to the lower airways hastens spread to the lower respiratory tract (Domachowske & Rosenberg, 1999).

Forty to fifty percent of infants with upper respiratory symptoms will develop lower respiratory tract disease (Lugo & Nahata, 1993). Two to three days after onset of initial upper respiratory tract symptoms, lower respiratory tract symptoms begin. Tachypnea, wheezing with prolonged expiratory phase, and rales represent viral spread into the lower bronchi and bronchioles (Domachowske & Rosenberg, 1999). Dyspnea and increased work of breathing manifested by nasal flaring, restlessness, substernal and intercostal retractions are prominent features. Typically the breathing pattern is shallow, with respirations between 40 and 60 breaths per minute. (Schwartz, 1995; Jeng & Lemen, 1997).

Irritability, poor feeding and vomiting are common (Jeng & Lemen, 1997). Dehydration due to increased insensible losses from fever and hyperventilation coupled with anorexia can result in significant fluid deficits (Boyer, 1999). Abdominal distention due to pulmonary hyperinflation with palpable liver and spleen below the costal margin (Jeng & Lemen) completes the picture.

Hypoxia is the most devastating consequence of bronchiolitis (Rakshi & Couriel, 1994). Difficult to detect clinically, hypoxemia tends to be more marked than anticipated on the basis of clinical findings (Schwartz, 1995). Children are frequently hypoxemic due to bronchiolar obstruction and vasodilation of pulmonary vessels around alveoli that remain poorly ventilated (Lugo & Nahata, 1993). Noninvasive oxygen saturation monitoring may be the single best predictor of severity of bronchiolitis (Schwartz).
Anterior-posterior chest radiograph is normal in 50% of children with bronchiolitis (Schwartz, 1995). Children with moderate to severe disease show hyperinflation, flattened diaphragms, patchy pulmonary infiltrates and segmental atelectasis (Jeng & Lemen, 1997; Evans et al., 1998). Pleural effusion is rare (Schwartz, 1995).

Nasal pharyngeal aspirate for direct fluorescent antibody or enzyme-linked immunooassay will quickly reveal if respiratory syncytial virus is the etiological agent. A viral respiratory panel for respiratory syncytial virus, influenza types A and B, parainfluenza types 1, 2, and 3, and adenovirus will give definitive, if delayed, etiology. These tests allow detection directly in respiratory secretions, and may help direct treatment (Englund, Pedro, Piedra, & Whimbley, 1997).

The severity of illness is difficult to assess. Capillary blood gases and pulse oximetry are valuable tools for assessing the severity of respiratory distress. Pulse oximetry is the most reliable method to assess the severity of illness, respiratory compromise (Schwartz, 1995; Mai, Selby, Simpson, & Isaacs, 1995), and oxygen needs in bronchiolitis. Oximeters provide continuous, instantaneous and non-invasive measures of arterial oxygen levels (Rakshi & Couriel, 1994). Oxygen saturation is diminished in almost all who are moderate to severely ill (Jeng & Lemen, 1997). Saturations below 90-92% indicate severe bronchiolitis (Welliver, 1998). See Table 5.

The respiratory rate can be used to help determine severity of disease (Lukic-Grlic et al., 1999). Respiratory rate is inversely related to oxygen levels in the blood except when respiratory failure is eminent (Welliver, 1998). Increased respiratory rate signals
low levels of oxygenation. Severity of illness is indicated by decreased oxygen
saturation, the need for oxygen therapy and increased respiratory rate.

Other clinical signs correlate poorly with hypoxemia (Rakshi & Couriel, 1994).
Findings such as fever, skin color, wheezes, chest wall retractions, and crackles are
variable in relation to the degree of hypoxemia as measured by pulse oximetry (Welliver,
1998).

Deciding when to hospitalize a sick infant is difficult. Children require
hospitalization when apnea occurs, fluid intake is impaired and the child is at risk for
dehydration or aspiration, moderate respiratory distress is noted, saturations are less than
92%, the age of the child is less than two months, or underlying conditions are present
(Hanson & Shearer, 1999).

Resolution of bronchiolitis may be uncomplicated or may involve repeated
episodes of symptoms of reactive airway disease. Most previously healthy infants suffer
severe signs and symptoms for 48 to 72 hours and are completely well in two to three
weeks (Schweich, 1994). Children with chronic cardiopulmonary, congenital, metabolic
or neurologic disorders or those who have a gestational age less than 36 weeks suffer a
more protracted course (Long, 1999).

**Differential Diagnosis**

Differential diagnosis of a child with wheezing can be difficult. Clinical
similarities exist in all diseases that produce wheezing. A complete history of the
problem can provide clues to the diagnosis. See Table 6.

Asthma is the most common cause of wheezing in infants (Hiatt, 1994) and very
difficult to differentiate from bronchiolitis (Mamlock, 1997). The first episode of
wheezing in an infant with a viral trigger is usually deemed bronchiolitis, recurrent episodes are usually termed asthma. Wheezing is a common symptom in the first three years of life. Defined by a largely reversible inflammatory process of the lower respiratory tract, asthma is manifested by recurrent obstruction of airflow. Pathology includes epithelial denudation, mucosal edema, viscid secretions (Bogunicwicz & Leung, 1999), and increased responsiveness of bronchial smooth muscle associated with environmental, allergic and respiratory viral stimuli (Hiatt, 1994). First asthmatic episodes usually follow the onset of a viral infection by a few days. Viruses continue to be the principal triggers of asthma throughout life. Signs and symptoms include cough, wheezing, dyspnea, intercostal and suprasternal retractions. Chest radiograph shows bilateral hyperinflation, bronchial thickening, flattening of the diaphragms, patchy atelectasis, and peribronchial infiltrates. Sputum smear shows clumped eosinophils. Eosinophilia is also commonly found in the blood. Treatment includes inhaled beta agonists to relieve acute bronchoconstriction and inhaled or oral anti-inflammatories to reduce inflammation (Bogunicwicz & Leung, 1999).

Pneumonia presents with a history of fever, coryza, and cough, then progresses to wheezing, rales and dyspnea including retractions, grunting and nasal flaring (Larsen et al., 1999). Defined as an inflammation of the lungs caused by bacteria, viruses and chemical irritants, pneumonia constitutes the majority of pediatric pulmonary infections. Pathology includes exudative fluid filling the alveolar air sacs and invasion of the alveolar septa by inflammatory cells (Schumann, 2000). Chest radiograph shows perihilar streaking, increased interstitial markings, peribronchial cuffing, bronchial pneumonia or lobar consolidation (Larsen et al., 1999). Sputum for culture shows a
bacterial pathogen when one is present, and mixed bacterial population (Boyer, 1999).

Nasal washing for direct fluorescent antibody or enzyme-linked immunoassay and viral
culture reveal the viral pathogen. Treatment includes antibiotics if bacterial,
supplemental oxygen, inhaled bronchodilators, and supportive care (Larsen et al., 1999).
Continuing fever and persistent rales helps differentiate pneumonia from bronchiolitis.

Gastroesophageal reflux can result in indirect tracheal aspiration and wheezing
due to inflammation (Sondheimer, 1999), or obstructive apnea due to laryngospasm.
Defined as retrograde movement of gastric contents from the stomach to the esophagus,
reflux is manifested clinically as coughing, choking or effortless regurgitation of a
portion of the feeding in the immediate postprandial period. Pathology includes the
dysfunction or incoordination of the mechanisms of the upper gastrointestinal tract
probably as a result of the delay in the maturation of this function. Reflux is problematic
in children with chronic problems such as symptomatic cardiopulmonary, neuromuscular
and immunologic diseases (Belnap & McEvoy, 1994). Chest radiograph typically shows
perihilar streaking with a right upper, lower or both infiltrate (Hiatt, 1994). Barium
swallow assists in confirming the status of anatomy, motility and swallowing functions.
Gastric scintiscan allows visualization and documentation of gastroesophageal reflux and
actual aspiration. Five channel pneumocardiogram with pH probe allows 12 to 24 hours
to study graphed esophageal pH variance with respiratory response. Bronchial-alveolar
lavage tests for lipid laden macrophages that are found only when aspiration of a fat
containing substance has occurred. Therapy includes upright positioning during and after
feeding, thickened feeds and possible pharmacology with histamine 2 receptor blocking
agents (Belnap & McEvoy). Intermittent episodes of wheezing associated with feeding
without a history of upper respiratory infection helps swing the pendulum toward
gastroesophageal reflux and away from bronchiolitis.

Foreign body aspiration is heralded by acute onset of respiratory distress with
coughing, choking, and wheezing without sign of upper respiratory infection (Mamlock, 1997). Children most often affected are six months to three years. Physical findings are
asymmetric with unilateral diminished breath sounds or wheezes. History includes an
object or food in the mouth with activity. Retrospective studies suggest that peanuts and
tree nuts are the most common objects found. Chest radiograph may or may not show a
lucency in the trachea. Usually, unilateral hyperinflation or atelectasis is seen with
inspiratory and forced expiratory films (Burton, Brick, Hall, Riggs, & Houston, 1999).
Definitive treatment is removal of the object with rigid bronchoscopy followed by
inhaled beta agonists and chest physiotherapy (Larsen et al., 1999).

Cardinal signs of congenital heart disease with congestive heart failure include
cardiac murmur, hepatosplenomegaly, and pulmonary edema, which include tachypnea,
dyspnea, rales and wheezing. Other signs include history of diaphoresis, feeding
associated with pallor and early fatigue, and poor weight gain. Defined as the failure of
the heart to meet the metabolic needs of the body, congestive heart failure from
congenital heart disease begins before age one in 10% of infants (Wolfe, Boucek,
Schaffer, & Wiggins, 1999). Pathology includes pulmonary congestion due to a large left
to right shunt (Hiatt, 1994). Chest radiograph shows enlarged cardiac silhouette (Hanson
& Shearer, 1999). Electrocardiogram and echocardiogram add rhythmic and structural
information about the heart. Treatment includes diuretics and possibly cardiac glycosides
(Talner, 1998). Surgical intervention is definitive when available.
Pertussis is a disease of the ciliated epithelium of the respiratory tract caused by Bordetella pertussis (Cherry, 1994). Early in the disease upper respiratory symptoms predominate with rhinitis, fever, sneezing and cough. Symptoms progress to paroxysmal choking and coughing that is related to thick tenacious mucus. Upper and lower airway obstruction, hypoxia and pneumonia may occur if the infant cannot clear the secretions (Hiatt, 1994). Differential white blood count shows a lymphocytosis. Nasal pharyngeal washing for direct fluorescent antibody reveals the pathogen. Chest radiology shows no change unless consolidation has occurred. Erythromycin is the treatment of choice. Bronchodilators and corticosteroids have also been used (Cherry, 1994). Diagnostic testing is the only way to accurately differentiate between pertussis and bronchiolitis.

Cystic fibrosis is an autosomal recessive disorder of the exocrine glands (Schumann, 2000). Recurrent or serious pulmonary infection with a significant reactive airway component including wheezing, cough and fever are common complaints. Mucus is abnormally tenacious, stools are bulky and profuse, and the child fails to gain weight normally (Larsen et al., 1997; Hiatt, 1994). Chest radiograph shows inflammatory changes. Sweat chloride level is elevated. Therapy includes bronchodilators, mucolytics, and chest physiotherapy to aid in expulsion of tenacious mucus and pancreatic enzymes to aid digestion (Hansen & Shearer, 1999).

Immotile cilia syndrome has an autosomal recessive mode of inheritance. Chronic upper and lower respiratory tract infections are common including sinusitis, otitis media, and pneumonia. Symptoms are recurrent due to the lack of mucociliary clearance. Pathology includes distal bronchiole obstruction and mucus plugging due to a defect in mucociliary transport caused by primary ciliary dyskinesia. Clinically seen
symptoms includes wheezing, coughing, rales and dyspnea. Diagnosis is confirmed by biopsy of bronchial or occasionally nasal turbinate epithelium. Therapy is directed toward removal of bronchial secretions and prevention of respiratory complications. Treatment includes inhaled bronchodilators, mucolytics, chest physiotherapy and postural drainage (Cutler & Hawkins, 1994).

Congenital vascular anomalies are typically aberrant large blood vessels that partially obstruct the trachea or esophagus, which results in respiratory distress, cough and swallowing dysfunction. Vascular rings and slings become symptomatic during the first year of life causing recurrent cough, wheeze and feeding disorders (Hiatt, 1994). Barium swallow is the mainstay of diagnosis as it demonstrates esophageal compression. Bronchoscopy allows visualization of tracheal compression. Surgical correction when available is definitive (Larsen et al., 1999).

Treatment

Significant advances have been made during the last 40 years in our understanding of the pathophysiology, epidemiology, and immunology of bronchiolitis. Despite increased enlightenment, there continues to be a fair amount of controversy regarding the optimum management of the child with bronchiolitis (Domachowske & Rosenberg, 1999). Current therapy remains largely supportive. Effective treatment should have as its’ goals to avoid or shorten hospital admissions, reduce the number of outpatient visits without jeopardizing the health and well being of the child, and reduce the burden on the parents due to lost sleep and lost wages. Treatment must be cost effective to be useful, efficacy, side effects, adverse events, and the cost benefit ratio must be taken into account (Guerguerian, Gauthier, Lebel, Farrell, & Lacroix, 1999).
Despite the inevitability of these yearly epidemics, the associated health cost, and the considerable morbidity, therapy has remained essentially unchanged for more than 30 years. The observation made by Reynolds and Cook in 1963 that oxygen is vitally important and there is little evidence that any other therapy is useful in the treatment of bronchiolitis, is essentially true today.

Supportive home care includes vigorous nasal suctioning prior to feeding. The infant is an obligate nasal breather and will select breathing over eating. Nasal suctioning with saline nose drops prior to offering oral fluids may allow the infant to coordinate the suck swallow breath mechanism and help prevent dehydration (Bar-on & Zanga, 1996). Offering small frequent meals to avoid an overly full stomach and distended abdomen may decrease respiratory compromise and prevent aspiration. Smoking must be prohibited in the home, as well as kerosene heaters and woodburning stoves if not the primary heat source. Large particles from these burning sources are inhaled and further obstruct small airways. Other air pollutants and cold air should also be avoided to reduce the risk of increased bronchoconstriction (Jeng & Lemen, 1997). Antipyretics for fever and irritability may be utilized (Schweich, 1994). Teaching caretakers to recognize worsening respiratory status and reevaluation in 24 hours is essential.

Supportive hospital care includes cool humidified oxygen to relieve hypoxemia and reduce insensible water loss from tachypnea (Bar-on & Zanga, 1996). Supplemental oxygen is the therapeutic mainstay of bronchiolitis worldwide (Halfaer et al., 1996). Monitoring saturations with pulse oximetry is necessary to keep saturations above 92 to 95%. Positioning of the infant is of great importance, semi-fowler's position with the head and chest elevated 30-40 degrees, and the neck slightly extended is the position of
choice (Welliver 1998). Euvolemic status needs to be carefully maintained. Nasogastric feeds to supplement oral feeding, or intravenous maintenance fluids will prevent dehydration. Avoiding overhydration will help prevent the risk of pulmonary edema, or transudation of fluid into alveolar or interstitial spaces (Halfaer et al., 1996). Frequent nasopharyngeal suctioning with saline nose drops will help keep the nasal passages clear and reduce work of breathing (Bar-on & Zanga, 1996). Electrolytes should be carefully monitored in the infant with severe bronchiolitis and rising carbon dioxide levels due to increased secretion of antidiuretic hormone and the resulting hyponatremia (Rakshi & Couriel, 1994). Antipyretics may be utilized for fever or irritability, if necessary (Schweich, 1994). Minimal handling and early recognition and treatment of complications are the foundation of supportive care (Rakshi & Couriel, 1994).

Wide ranges of pharmacological agents are available for use to assist in the treatment of a child with bronchiolitis. Efficacy in the use of these agents with bronchiolitis is controversial. Nebulized albuterol is a selective beta-2 agonist whose peak effect is 15 minutes, and duration is 3 to 4 hours. Available since the 1950s, albuterol relaxes pulmonary smooth muscle, reduces airway resistance, suppresses inflammatory mediators from mast cells, decreases microvascular permeability, and enhances mucociliary action (Klassen, 1997). Infants have a paucity of smooth muscle in their pulmonary system (Welliver, 1998), so they are less likely to benefit from smooth muscle relaxation (Klassen). Research has shown that 30 to 50% of infants will demonstrate a significant short-term improvement in clinical scores, air flow, and oxygenation (Wang, Kellner, Ohlsson, & Gadomski, 1999). No evidence exists that albuterol reduces duration of illness, admission rates or decreases length of
hospitalization (Rakshi & Couriel, 1994; Klassen, 1997). Albuterol is considered safe, but conclusive evidence of its efficacy is lacking (Flores & Horwitz, 1997; Randolf, 1999). Gauging clinical response after a trial of nebulized albuterol is reasonable therapy for a child with bronchiolitis (Halfaer et al., 1996; Dobson et al., 1998).

Nebulized racemic epinephrine is a mixed alpha and beta adrenergic whose peak effect is 30 minutes, and duration is 2 hours. Reducing bronchial secretions and mucosal edema is the alpha effect of racemic epinephrine. Beta adrenergic response is smooth muscle relaxation and inhibition of mast cell mediated inflammation (Klassen, 1997). Available since the 1970s, nebulized epinephrine results in significant improvement in clinical scores, airway resistance in children, and oxygenation, when compared with beta-2 agonists. Research has shown a decreased length of stay in the emergency department and admission rate to the hospital when racemic epinephrine is used. Reduced bronchial edema is credited with the positive results (Jeng & Lemen, 1997).

Systemic glucocorticoids are anti-inflammatories that reduce swelling and edema in the bronchial tree and cause some vasoconstriction. Research has shown no therapeutic advantage or disadvantage to the use of steroids, study results are inconsistent (Klassen, 1997). Population statistics demonstrate the lack of efficacy of steroids in bronchiolitis, but when taken separately, some individuals do respond favorably to steroid therapy (Halfaer et al., 1996). Steroid use is warranted for patients with previously documented reactive airway disease (Klassen, 1997).

Inhaled glucocorticoids reduce bradykinin induced vascular permeability. Only one to five percent of the drug reaches lung periphery. Neither symptoms of acute bronchiolitis or post bronchiolitic sequelae were reduced with inhaled glucocorticoid use.
Benefits for bronchiolitis patients are unknown (Richter & Seddon, 1998; Fox et al., 1999).

Antibiotics include a huge range of antimicrobials. Risks of secondary bacterial infection including septicemia and pneumonia in the infant with bronchiolitis are less than two percent (Kupperman, 1998; Greenes & Harper, 1999). Bacterial acute otitis media is a frequent complication of bronchiolitis, 57 to 67% positive, and if found can be treated with oral antibiotics. Use of antibacterial agents in a child with typical viral bronchiolitis is futile and routine use of antibiotics is discouraged (Halfaer et al., 1996). Children less than two months of age who focalize symptoms poorly, or children who present with atypical clinical symptoms may be started on antibiotics initially until all cultures are negative (Klassen, 1997).

Aerosolized ribovirin is a synthetic nucleoside antiviral that inhibits viral replication (Piedra, 1997). Licensed in 1985, the precise mechanism of action is unknown (Domachowske & Rosenberg, 1999). Ribovirin is expensive and difficult to use, due to complex scheduling (Feldstein, Swegarden, & Atwood, 1995). The American Academy of Pediatrics (AAP) has changed its’ recommendation from “should be used” to “may be considered” (AAP, 1996). Efficacy is questionable, a recent meta-analysis showed no benefit. Ribovirin therapy does not lead to improvement in clinically important outcomes (Randolf, 1996; Guerguerian et al., 1999), such as shortening hospital days, avoiding mechanical ventilation or death (Welliver, 1998).

RSV-IGIV (Respigam) is a polyclonal hyperimmune globulin containing high titers of respiratory syncytial virus antibody. Immerging as a treatment modality for the
high-risk child, respigam has not revealed any significant therapeutic effect (Welliver, 1998).

Many different forms of treatment are available for acute viral bronchiolitis. Most are unproven or are of limited benefit (Rakshi & Couriel, 1994). European and United States' practices show a predilection for using bronchodilators, corticosteroids and antibiotics in infants hospitalized for bronchiolitis (Kimpen & Schaad, 1995; Behrendt, Decker, Burch & Watson, 1999). No evidence exists that any treatment reduces the incidence of subsequent respiratory problems common after acute viral bronchiolitis.

**Prevention**

Most viruses including respiratory syncytial virus are transmitted by direct contact or aerosolized nasal secretions and are easily spread. To prevent inoculation one must be at least six feet away from an infected individual. Avoidance of infected persons is the best prevention but not always easy due to viral shedding (Jeng & Lemen, 1997). Avoiding infected individuals is difficult, because the virus is shed for one to two days before symptoms appear and for three weeks after the development of symptoms (Domachowske & Rosenberg, 1999). Inoculation by infected respiratory secretions, direct contact or aerosolized large droplets, and typically occurs through the nasal or conjunctival mucosa (Long, 1999; Meissner et al., 1999). The mouth is much less sensitive, as a portal of entry. Hands of family members are the most important vectors for spread of infection to the infant. Viruses can survive on the hand for 30 minutes or longer. Consistent handwashing appears to be a very good method of preventing viral spread (Jeng & Lemen, 1997).
RSV-IGIV (Respigam) approved in 1996 (O’Shea et al., 1998) is a pooled polyclonal hyperimmune globulin containing high titers of respiratory syncytial viral neutralizing antibodies administered monthly in an intravenous infusion. Respigam has been shown to provide a 41% reduction in hospitalization in the high-risk pediatric population. Additional protection against other respiratory viral illnesses is also conferred (Meissner et al., 1999). Immune globulin may be recommended for infants with pre-maturity, chronic lung disease, and is preferred for children with immunosuppression (Englund et al., 1997), but it is contraindicated for children with cyanotic congenital heart disease due to unexplained deaths (Simoes, Sondheimer, & Too, 1998; Domachowske & Rosenberg, 1999). Respigam has not been shown to have an effect on mortality (O’Shea et al., 1998). It is dosed at 750 milligrams per kilogram and costs approximately 1000 dollars per dose due to the hospital stay that is involved for infusion (Meissner et al., 1999). Side effects include those that involve immunoglobulin infusions including fever, labile blood pressure and desaturations due to fluid overload (Domachowske & Rosenberg, 1999; Meissner et al., 1999). Administration of live vaccines are withheld during Respigam infusion due the inactivation of the vaccine by immunoglobulin (Meissner et al., 1999).

Palvizumal (Synergis) first approved for the 1998-99 respiratory season is a monoclonal antibody for respiratory syncytial virus (Domachowshe & Rosenberg, 1999). Administered monthly during winter and spring months as an intramuscular injection, Synergis has demonstrated a 55% reduction in the risk of hospitalization in high-risk pediatric patients. Synergis has been shown to provide benefit for infants who are 28 to 35 weeks gestation at birth, and infants who have chronic lung disease. The injection is
not recommended for children with cyanotic heart disease. Synergis is dosed at 15 milligrams per kilogram and costs about 1200 dollars per dose. Live vaccine administration like varicella, measles, mumps, and rubella are not contraindicated with Synergis treatment. Side effects related to Synergis are rare (Meissner et al., 1999).

**Future**

Bronchiolitis may result in serious respiratory disease and respiratory failure. Research is progressing toward the goal of a safe and effective vaccine that is not limited in use, but is able to protect all infants from a disease that has been associated with ongoing respiratory morbidity and has the potential to be life threatening (Hall, 1999). Several studies are in progress using a purified fusion protein preparation as a vaccine for children with chronic lung disease. This same preparation is also being used to vaccinate breast feeding women with the hope of protecting neonates from respiratory syncytial virus during the first critical months of life (Hussell & Openshaw, 1999). Results are promising.

Antiviral compounds for use against the viruses are being developed and are considered to hold great promise. One, RD6-2198 interacts with the viral envelope; another targets the 2-5A dependent RNAase L to the antisense specific RNA. This drug is 50 to 90 times more potent against RSV A2 than Ribovirin (Hussell & Openshaw, 1999).

There have been significant advances in the understanding of chemokine induced inflammatory responses of the host to viral infections, but the significance of the responses is largely uncharted. Numerous studies are being undertaken to try to explain
the specific pathway that leads to the inflammatory responses that precipitate an augmented illness (Jaovisidha et al., 1999).

Surfactant abnormalities occur in bronchiolitis and may represent one of the pathophysiological mechanisms causing airway obstruction (Dargaville, South, & McDougall, 1996). Pulmonary surfactant becomes dysfunctional and is not produced during acute viral bronchiolitis. Surfactants’ role in the development of airway obstruction in bronchiolitis and the potential role of exogenous surfactant treatment deserve further investigation (Nelson, 1997).

Trials with a rat model are underway using aerosolized interferon-gamma to alter the inflammatory response and attenuate the postviral sequelae. Positive results have been attained thus far but future studies will more directly address if treatment with interferon-gamma reversed deficiencies or created a supraphysiologic pharmacologic effect (Sorkness et al., 1999).

Heliox, a mixture of 80% helium and 20% oxygen, has been successfully used as a treatment for asthma and has been suggested as a potential therapy in bronchiolitis. Bronchiolitis has a similar pathophysiology to asthma with increased airway resistance and turbulent gas flow. Heliox decreases work of breathing, respiratory distress and may avert intubation (Barnes, 1998) by perserving laminar flow at high flow rates due to the increased density of helium (Hollman et al., 1998).

Conclusion

Immunopathogenesis of viral bronchiolitis remains mostly unknown. The link between bronchiolitis and chronic airway dysfunction is complex.
Obstacles to preventing and controlling bronchiolitis remain considerable and challenging. Preventing bronchiolitis remains a high priority to reduce morbidity. Prophylaxis needs to be available to all, at a reasonable cost, that is feasible in a variety of healthcare settings, and accepted by primary medical caregivers. To protect our susceptible populations, prophylactic approaches to bronchiolitis must be optimized.

Controversy continues over essentially all the therapeutic approaches to bronchiolitis. Treatment remains limited, debatable, and mostly supportive. Questions remain regarding the efficacy, safety and the cost-benefit ratio of therapeutic interventions. Continuing research into the pathophysiology, immunology, and therapeutics of bronchiolitis may help answer these questions. Investigations continue to try to find the best treatment regime.

Hospitalization, especially intensive care, is the largest short-term expenditure associated with bronchiolitis. Reducing hospital days required or decreasing the need for hospitalization without endangering health status will mean fewer health care dollars expended. Answers to many questions need to be accomplished before this goal can be achieved. Acute viral bronchiolitis still merits our respect and close attention.

Morbidity and mortality associated with bronchiolitis, coupled with worldwide distribution make it a prime target for enhanced research for the development of an effective vaccine. Progress is being made in this area. Research continues, but no effective vaccine is available to date.

Prevention of long term pulmonary complications from avoidance of severe bronchiolitic illness early in life is a primary goal. The benefit of parental education in bronchiolitis exposure prevention and early treatment intervention is unmatched.
Reduced pulmonary morbidity, decreased hospitalization days and lowered health care costs will be the rewards.
Bibliography


### Table 1

<table>
<thead>
<tr>
<th>Risk Factors for Bronchiolitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Environmental exposure to Tobacco Smoke</td>
</tr>
<tr>
<td>- Birth Order</td>
</tr>
<tr>
<td>- Birth Month</td>
</tr>
<tr>
<td>- Family history of Atopy or Asthma</td>
</tr>
</tbody>
</table>

(Reese, 1992; Panitch, 1993; Lugo, 1993; Baron, 1996; Hiatt 1997; Mamlock, 1997; Dybing, 1999; Moreno, 1999)
### Table 2

**Risk Factors for Severe Bronchiolitis**

- Chronic pulmonary disease
- Complicated or Cyanotic heart disease
- Immunocompromise
- Gestational age less than 36 weeks

(Boeck, 1996; Baron, 1996; Mamlock, 1997; Piedra, 1997; O'Shea, 1998)
Table 3

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Etiological agents of Bronchiolitis</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Respiratory syncytial virus A and B</td>
<td>40-75</td>
</tr>
<tr>
<td></td>
<td>Parainfluenza type 1 and 3</td>
<td>15-30</td>
</tr>
<tr>
<td></td>
<td>Rhinovirus</td>
<td>3-10</td>
</tr>
<tr>
<td></td>
<td>Adenovirus type 3, 7, and 21</td>
<td>3-10</td>
</tr>
<tr>
<td></td>
<td>Influenza A and B</td>
<td>3-10</td>
</tr>
<tr>
<td></td>
<td>Mycoplasma pneumoniae</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

(Panitch, 1993; Denny, 1995; Halfaer, 1996; Welliver, 1998; Anderson, 1998)
### Table 4

**Bronchiolitis Time Line**

<table>
<thead>
<tr>
<th>Day</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Inoculation</td>
</tr>
<tr>
<td>3-7</td>
<td>Incubation, Upper respiratory tract illness</td>
</tr>
<tr>
<td>5-9</td>
<td>Lower respiratory tract illness</td>
</tr>
</tbody>
</table>

(Lugo, 1993; Schwartz, 1995; Larsen, 1997; Jeng, 1997; Welliver, 1998; Domachowske, 1999)
Table 5

<table>
<thead>
<tr>
<th>Bronchiolitic Symptoms for Severity of Illness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>MILD</strong></td>
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<tr>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>Respiratory Rate Depending on age</td>
</tr>
<tr>
<td>40 and below</td>
</tr>
<tr>
<td>40 - 60</td>
</tr>
<tr>
<td>60 and above</td>
</tr>
<tr>
<td>RA SPO2</td>
</tr>
<tr>
<td>92-100</td>
</tr>
<tr>
<td>92-95</td>
</tr>
<tr>
<td>&lt; 92</td>
</tr>
<tr>
<td>Hydration</td>
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<tr>
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<tr>
<td>60-100% normal</td>
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<tr>
<td>&lt; 60% normal</td>
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<tr>
<td>Skin color</td>
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<td>Variable</td>
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<tr>
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<tr>
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</tr>
<tr>
<td>Variable</td>
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<td>Variable</td>
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<tr>
<td>Variable</td>
</tr>
</tbody>
</table>

(Rakshi, 1994; Schwartz, 1995; Jeng, 1997; Welliver, 1998; Lukic-Grlic, 1998)
# Table 6

<table>
<thead>
<tr>
<th>Disease</th>
<th>Definition/Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchiolitis</td>
<td>Inflammation of the small bronchioles with obstruction of airflow characterized by abrupt onset dyspnea and wheezing in an infant. NP wash for DFA reveals etiology.</td>
</tr>
<tr>
<td>Asthma</td>
<td>Largely reversible inflammatory process of the lower respiratory tract manifested by recurrent obstruction of airflow characterized by wheezing, cough or dyspnea.</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Acute inflammation of lung tissue. Chest x-ray shows patchy infiltrates or lobar consolidation.</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>Retrograde movement of gastric contents from the stomach into esophagus with possible tracheal aspiration and wheezing occurring in the postprandial period. Five channel pneumocardiogram with pH probe confirms diagnosis.</td>
</tr>
<tr>
<td>Foreign Body Aspiration</td>
<td>Acute onset of coughing and choking without signs of URI. Unilateral diminished breath sounds and wheezing may be present. Diagnosis usually confirmed by asymmetrical atelectasis or hyperinflation seen on inspiratory or forced expiratory chest x-ray.</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>Failure of the heart to meet the metabolic needs of the body characterized by cardiac murmur, dyspnea, hepatospleenomegaly and feeding difficulties. Diagnosis by ECG and echocardiogram.</td>
</tr>
<tr>
<td>Pertussis</td>
<td>Loss of ciliated epithelium in respiratory tree characterized by paroxysmal cough and choking. NP for DFA reveals pathogen.</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>Disorder of exocrine glands characterized by respiratory distress and profuse bulky stools. Elevated sweat chloride level is diagnostic.</td>
</tr>
<tr>
<td>Immotile Cilia</td>
<td>Autosomal recessive disorder of ciliary dyskinesia characterized by recurrent upper and lower respiratory infections. Diagnosis confirmed by bronchial biopsy.</td>
</tr>
<tr>
<td>Vascular Rings/Slings</td>
<td>Aberrant large vessel anatomy characterized by respiratory distress, cough, or swallowing dysfunction. Barium swallow demonstrates esophageal compression, bronchoscopy allows visualization of tracheal compression.</td>
</tr>
</tbody>
</table>

NP = Nasopharyngeal  
DFA = Direct Florescent Antibody  
URI = Upper Respiratory Infection  
ECG = Electrocardiogram