



## BRONCHIOLITIS

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### I. INTRODUCTION

The term *bronchiolitis* was first used in 1940 to describe a condition specific to children that was hypothesized to be of viral origin. Not until 1960 was a connection established between the virus retrieved from chimpanzees (1) and children (2) with lower respiratory disease. Thus, bronchiolitis in children under 1 year old was initially named “chimpanzee coryza agent;” later the virus was designated respiratory syncytial virus (RSV).

Bronchiolitis is defined as inflammation of the bronchioles (3). Based on clinical findings, the disease is diagnosed in children under 24 months who undergo a first bout of obstruction in the lower respiratory tract. Diagnostic criteria vary widely.

From the clinical standpoint, acute bronchiolitis or viral acute bronchiolitis is an infectious syndrome that first appears in the upper respiratory tract (such as coryza, sniffles, and nasal obstruction) and progresses to the lower respiratory tract with cough, expiratory distress, chest retractions, diffuse coarse crackles, and wheezing. American literature emphasizes the presence of wheezing more than European authors. In diagnoses, it is quite frequently confused with the first asthmatic attack presented by a child. Current debate over diagnostic criteria hinges on such factors as age, indications of pneumonia, respiratory difficulty, and atopy (4).

## II. ETIOLOGY

The etiology of bronchiolitis is viral in the majority of cases, especially in developed countries where the causative agents of wheezing following infections are respiratory viruses. RSV is the most common etiologic agent, although other viruses and agents such as *Bordetella pertussis*, *Chlamydia trachomatis*, *Mycoplasma pneumoniae*, and *Moraxella catarrhalis* may be identified (5-9). Fischer (10) analyzed 128 hospitalized cases in R o Grande do Sul, Brazil, and found RSV in 52% of the cases, parainfluenza in 5.1%, adenovirus in 1.4%, and rhinovirus in 0.9%. The RSV A serogroup is related to more severe clinical manifestations of bronchiolitis (11).

Secondary bacterial infection after RSV injury may not always be common, but in developing countries there is some evidence that it follows certain viruses. Viral respiratory infections influence several aspects of the host's defenses and pave the way for subsequent acute bacterial infection (12). Thus, RSV pneumonia is sometimes difficult to differentiate from bronchiolitis. It may allow the secondary bacterial infections to develop (13).

In a prospective study, Korppi et al. (7) concluded that either viral or bacterial infections can occur with wheezing in toddlers. Bronchiolitis characteristically occurs in children under 2, primarily in infants in developing countries (13, 14). In urban areas of the United States, 50% of children under 1 year and almost all 2-year-olds have been infected by RSV (11).

## III. EPIDEMIOLOGY

RSV, the major cause of acute bronchiolitis, can be associated with other respiratory viral syndromes such as tracheobronchitis and pneumonia. Many authors have drawn attention to the seasonal aspect of RSV, with peak incidence in periods of low temperature. Dawson et al. (15) described epidemics in New Zealand, with major hospital admissions in winter and spring. In the state of R o Grande do Sul, Brazil, a five-year review in a pediatric hospital showed that 80% of the cases seen in clinics were from June to August, the coldest months of the year (5). In R o de Janeiro, RSV attacks usually occur in autumn. This accounts for an increased demand on health services for treatment of acute respiratory infections (ARI), sometimes severe enough to require emergency care (16, 17).

In Benin, Nigeria, cases were most frequent in rainy months (18). Similar findings were related by Cherian et al. (6) in South India, where he found greater occurrence of bronchiolitis or other diseases caused by RSV in the rainy season and emphasized that in tropical Asia the population usually stays more confined to the home during this period. Such is also the case in winter in temperate countries, which makes it easier for the virus to spread. High humidity in the air and abrupt daily variations in temperature, as observed in the epidemic in Shanxi, might contribute to the survival of RSV in the environment. In this study, household size influenced the number of registered cases (i.e., the smaller the household, the greater the incidence of bronchiolitis) (19).

Bronchiolitis may be more common in males (5, 19, 20), although Whol (3) assigned an equal distribution of the disease among both sexes, but found severe cases occurring more often in boys. Children that attend daycare centers may have a greater risk of becoming infected, given their close contact with others in a confined area (20, 21). Some historical and demographic studies have yielded contradictory results (22). Others report that crowding, the presence of older siblings, having a resident smoker in the house, family history of allergies or asthma (23), and the absence of breast-feeding (24) constitute factors that increase the probability of acquiring bronchiolitis.

Environmental conditions, although often commented on, are hard to prove as risk factors in respiratory infections. Recently, Morris et al. (25) in studying Navajo children found a larger number of patients with acute bronchiolitis in homes with wood-burning stoves. A retrospective study with children previously suffering from bronchiolitis, designed to detect subsequent wheezing, did not show any influence of parental smoking habits or socioeconomic status as risk factors for these episodes (26). These data appear to contradict another study that tried to classify risk factors for wheezing using multivariate analysis and concluded that previous episodes of bronchiolitis in the first years of life and passive smoking were important in the development of wheezing in children between 8 and 13 years of age (27). Bronchiolitis risk factors frequently described in literature include: prematurity, bronchopulmonary dysplasia, and cardiopulmonary diseases (5, 11, 21, 28-31).

Hall and McBride reported that 95,000 children are hospitalized each year in the United States because of RSV infection, with more than 4,500 fatal cases (21). Some reports vary greatly in their description of bronchiolitis lethality, with values ranging from 1.25 to 25% (25).

#### IV. PATHOGENESIS

The type of injury and clinical manifestations of the respiratory tract induced by viral diseases are probably consequences of the combination of the viral affinity for specific cells in segments of the airways (tropism), the destructive effect at the cellular level (virulence), the size of the respiratory passage in the host, and the immunologic response elicited. Although RSV is one of the least destructive of the respiratory viruses *in vitro*, its high affinity for the bronchial epithelium explains the tendency to produce major respiratory disease.

Inoculation of RSV presumably occurs through the nasal mucosa surface. After an asymptomatic incubation period of 4-5 days, the infected child develops characteristic symptoms of upper respiratory infections. The infection usually resolves spontaneously. Spreading to the lower respiratory tract is caused by mechanisms still poorly understood, presumably through aspiration of infected secretions which produce pneumonia or bronchiolitis (9).

From the anatomical standpoint, the mechanism that accounts for airway injury is the direct viral cytopathic effect following virus-host cell interaction and indirect effects mediated by immunologic mechanisms.

The primary immune response consists of tissue infiltration by recruited polymorphonuclear leukocytes and macrophages after the release of chemical messengers from damaged epithelial cells. These cells release more mediators, which alter endothelial permeability, epithelial junctions, and ion transport, thereby exacerbating inflammation with additional cell recruitment and promoting edema (33). The increased luminal contents with secretions and cellular debris account in part for airway obstruction, limiting air flow, and producing atelectasis and a consequent ventilation-perfusion mismatch.

Smooth muscle contraction is another mechanism of airway obstruction. Besides abnormalities of the adrenergic and cholinergic systems during respiratory virosis, the non-adrenergic non-cholinergic system (NANC) can also induce bronchoconstriction following epithelial damage (34). Neuropeptides are the chemical mediators of this system. Some of them (e.g., substance P, tachykinins, and calcitonin gene-related peptide [CGRP]) have the potential of inducing obstruction, but their role in bronchiolitis requires further elucidation (35).

Autopsy findings showed coexistence of IgG and a few RSV antigens in bronchiolitis in the lower respiratory tract, in contrast with the absence of immunoglobulin and abundance of viral antigens in infants dying with RSV pneumonia (34). The authors suggested that the disease might be induced by the Gell and Coombs type III allergic reaction.

In children with wheezing following RSV infection, specific IgE and high levels of histamine were found in their nasopharyngeal secretions to a greater degree than in children with other symptoms (36). Specific antibodies of the IgE and IgG4 classes were also found in the serum (37).

The decrease of T-suppressor lymphocytes with increased T-helper/T-suppressor ratios could play a role in the pathogenesis of acute bronchiolitis, allowing IgE hyperproduction and alveolar mast cell activation (38).

The specific cell response to RSV has been frequently described in the literature (39-42). This response seems to be more intense in children under six months (40) and in more severe cases (41). The possible relevance of delayed hypersensitivity is also suggested by the extensive mononuclear cell infiltrate. It was speculated that intrauterine sensitization with passage of a transplacental-transfer factor accounts for this exaggerated response in small children (43).

Some authors state that antigen-antibody complexes could participate in the pathogenesis of bronchiolitis. The maternal neutralizing antibodies against RSV, passively acquired by the fetus, might be responsible for the high incidence of the disease in the first months of life. Immune complexes could also be involved in the more severe disease presented by children who receive inactivated virus vaccines (44). Other findings contradict this hypothesis in reporting no correlation between passive and active antibodies and severity of the disease (45-48). Lamprecht et al. (46) suggested a qualitative difference between passive and vaccine-induced antibodies. Glezen et al. (49) in a prospective, randomized study of risk factors in bronchiolitis admitted that passive antibodies might be protective.

Santa Ana et al. (50) did not find low complement levels in the sera of patients with acute bronchiolitis. However, this cannot rule out the Gell and Coombs reaction in the pathogenesis of the disease.

The pathogenic mechanisms in bronchiolitis are still obscure. The ability to recover after RSV infection is related to IgA, IgG, and IgM secretory immunoglobulin levels and antibody-dependent, cell-mediated cytotoxicity (ADCC) (51-53). These mechanisms could account for the mild symptoms seen in reinfections. The variation in clinical findings in small children might result from underdeveloped individual host defenses (54).

## V. DIAGNOSIS

### a) Clinical and radiological diagnosis

Characteristic clinical manifestations yield the diagnosis in the majority of cases. Symptoms of the common cold, such as rhinorrhea, cough, low fever in the early stages, followed by respiratory distress with signs of bronchial obstruction and wheezing, are extensively appraised in the literature; some authors consider them as diagnostic criteria (5, 14, 55-57).

Clinical features may include moderate or high fever, often appearing 2 or 3 days after the beginning of flu-like symptoms. Coughs may be pertussis-like and, in severely ill patients, increased dyspnea and cyanosis occur, possibly evolving into respiratory failure (32).

The presence of cyanosis indicates severe hypoxia that can cause apneic spells (58). However, no correlation between clinical findings and the degree of hypoxemia has been reported. Hypoxemia in hospitalized children with severe symptoms almost always has a prolonged course. Arterial oxygen tension may return to the normal range 3 to 7 weeks after the beginning of clinical manifestations.

To identify indicators from patients' clinical histories, physical examinations, and laboratory findings, a prospective study involving 213 infants with bronchiolitis was performed (59). Six clinical and laboratory findings were identified as most strongly associated with subsequent disease severity. To wit:

- "very sick" or "toxic" appearance in child
- oximetry below 95% at rest;
- preterm birth before 34 weeks;
- respiratory frequency above 70 per minute;
- chest X-ray reveals atelectasis; and
- child under 3 months of age.

The cardiovascular findings are mainly determined by the degree of hypoxemia presented, although the relationship between RSV infection and supraventricular tachycardia in infants suggests direct viral action (60). Electrolyte disturbance, possibly severe, may also occur. Body fluid retention can be explained by the increased secretion of antidiuretic hormone (ADH), followed by hypernatremia resultant from secondary hyperaldosteronism. This elevated ADH secretion is probably appropriate and results from chest receptor responses to hypovolemia (61).

The age of the patient (infant up to 2 years) and whether this wheezing episode is his or her first must be considered. Recurrent bronchiolitis is rare, but presents a diagnostic dilemma.

Chest X-rays, although nonspecific, can provide complementary diagnosis. Visible radiographic manifestations include diffused lung hyperinflation with increased lung volume, hyperlucency, flattening of the diaphragms, and prominent bronchovascular markings with an interstitial infiltrate pattern. Atelectatic areas from mucoid plugging and low-density infiltrates are often seen, and pleural thickening may also be evident (3, 32, 58).

Chest X-rays are often of great value in patients hospitalized in intensive care. There are no clinical signs that distinguish between a child who has pneumonia and one who does not (6). Children can be classified as having a severe form of the disease, even with a normal chest radiograph, if they have severe respiratory distress, cyanosis, or gastrointestinal manifestations such as liquid refusal with vomiting or abdominal distention (62). Dawson et al. (63) found no correlation between radiographic findings and clinical manifestations in bronchiolitis. He suggested that chest X-rays should be obtained when intensive care is required, when subtle worsening of the respiratory status occurs, or with preexisting cardiac or lung disease.

It is frequently difficult to discriminate between the radiological findings of bronchiolitis and of viral pneumonia. Clinical-radiological diagnosis differentiates on the basis of increased respiratory effort involved in bronchiolitis. Some French authors have described these two processes as dyspnea-producing and non-dyspnea-producing bronchopneumopathies (32).

It is clear that, in some situations, the radiographic examination can show signs of bronchiolitis associated with more dense consolidations that suggest bacterial pneumonia leading to a diagnosis of both conditions (58). Friis et al. (64) emphasize the well-known troublesome radiographic differentiation between viral and bacterial infections. In their data, alveolar consolidations (lobar pneumonia) were found in both types of infections.

## **b) Laboratory diagnosis**

Epidemiological studies employ classical methods for RSV isolation in tissue cultures, attempting to provide specific viral etiology of community or nosocomial epidemics (65). This identification, obtained with specimens collected from nasopharyngeal aspirates, can be done where appropriate technology is in place. The procedure is less accessible in developing countries and has the drawback of taking a long time in obtaining results (66). In individual cases, a nasopharyngeal aspirate can be obtained and studied with the immunofluorescence technique, a highly sensitive method for RSV detection (62, 63, 66, 67).

Complement fixation permits the detection of specific antibodies (58, 68). It should be remembered that the absence of normal serological responses in small infants restricts the usefulness of this test (66, 69). Furthermore, two serum samples are necessary, with the second taken two weeks after the beginning of the symptoms, when the fourfold rise in the titer of antibodies should be observable (5).

## VI. DIFFERENTIAL DIAGNOSIS

Because wheezing is a major manifestation of bronchiolitis and other conditions in infants, differential diagnosis should consider many other diseases found in a wheezing baby.

The clinical criteria for bronchiolitis consist of the following upper respiratory tract manifestations: dyspnea, lung hyperinflation, crackles, and wheezing. The major differential diagnosis is asthma. This chronic affliction in small children can cause confusion with bronchiolitis, considering that viruses are the major precipitating factors of asthma attacks in this age group. Furthermore, children with a genetic predisposition to asthma with positive atopic family history can be infected by RSV and have bronchiolitis. It must be remembered that asthma is recurrent and often responds well to bronchodilators, while the same is not true in bronchiolitis. The child's predisposition to recurrent wheezing during viral episodes may have a genetic basis whether or not it is hereditary (70).

The role of hyperresponsiveness should be stressed. This term is used when there is an abnormal response with airway narrowing induced by nonspecific stimuli. Some authors discuss whether bronchial responsiveness determines wheezing episodes or if it is a sequela (71).

The other conditions that occur with wheezing also should be remembered, such as aspiration syndromes including gastroesophageal reflux, pulmonary malformations (cysts, tracheoesophageal fistulas), vascular ring, cystic fibrosis, foreign body aspiration, and other less common conditions. Usually, the medical history and eventual chest X-ray, along with contrast material in the esophagus if these conditions are suspected, are enough to establish the cause.

## VII. TREATMENT

Most cases can be treated on an outpatient basis with supportive care (i.e., rest, oral hydration, breast-feeding, appropriate clothing, warm baths, and antipyretics for fever).

The use of artificial ventilation is necessary only in a small percentage of children. Fischer (10) used it in 7.5% of his patients. Moderately or severely ill infants brought to health care units show wheezing. They are often treated with nebulized bronchodilators such as fenoterol, albuterol, or epinephrine, as recommended by the 1992 standardized Brazilian manual for acute respiratory infections (72).

Patients potentially at risk for developing severe forms of the disease are undernourished, dehydrated, premature, anemic, or those with cardiac disorders or previous apneic spells (5). In serious cases that require hospitalization, priority should be placed on treatment with humidified oxygen by any kind of available device: nasal cannula, facial mask, tent, or oxygen tent (Oxy-Hood®). Hypoxemia reversion frequently corrects the perfusion-ventilation disturbance that occurs in the disease. Often concentrations of only 35-45% oxygen are sufficient to improve the patient's condition (3).

In developing countries, arterial gasometry is often not feasible. However, even when available, it should not be performed in excess so as to avoid unnecessary suffering by the patient.

The optimal assessment of oxygen administration should be done by serial clinical evaluation, including the recording of vital signs, observations of sensorium, breathing patterns, perfusion, and the presence of cyanosis (5).

Nasal probes can be used with low flows of oxygen, 1 to 3 liters per minute. Oxygen tents (Oxy-Hood) are more suitable, but require higher flows, 8 liters per minute, and a compressor to blend the air. The continuous humidification of air by a vaporizer has not proven efficacious and therefore is not indispensable in the treatment of these patients. Fluid intake should be prescribed carefully due to the potential risk of lung edema and over-hydration. Ordinarily 70 to 80% of the daily recommended amounts are prescribed (3).

The use of drugs such as theophylline, sympathomimetics, anticholinergics, and corticosteroids is still controversial, and many authors do not encourage their use, because most studies have failed to demonstrate any effect on the natural course of the disease.

After the acute phase in children with persistent wheezing, oral inhalation of beclomethasone can be valuable in reducing the frequency of symptoms (73), but it is not a standard accepted procedure. Although respiratory physiotherapy is generally effective for clearance of bronchial secretions, no studies demonstrate its effectiveness in bronchiolitis (74).

Currently, the therapeutic use of human immunoglobulin G (IgG) is being attempted on an experimental basis to hasten recovery in infants with RSV bronchiolitis or pneumonia by lessening symptoms and curtailing the duration of viral shedding (75).

#### **a) Bronchodilators**

The administration of bronchodilator therapy in bronchiolitis is still controversial. The presence of wheezing often leads to the erroneous interpretation of the first asthma attack as bronchiolitis. In this situation, the use of bronchodilators could be beneficial.

Recently, two randomized, double-blind clinical trials showed opposing results with the use of nebulized albuterol. In one of them, Schuh et al. (76), in a study of 40 children between 6 weeks and 24 months, described clinical improvement involving the use of accessory muscles and oxygen saturations. Dosages of 0.15 mg/kg three times at 1-hour intervals were employed.

In another study with 21 infants, a drop in oxygen saturation was demonstrated in both albuterol and placebo groups. The duration and severity of desaturation were greater in patients that received albuterol (67). On the basis of these findings they concluded that the nebulized sympathomimetic drugs are not indicated in the treatment of bronchiolitis, despite the absence of significant adverse reactions to this drug.

Ipratropium bromide, a quaternary derivative of *N*-isopropylatropine, has been available for use since the early 1980s. It seems to be more bronchoselective and to produce fewer systemic anticholinergic side effects than atropine. The use of this drug in bronchiolitis has generated a new surge of interest. The first studies in the United Kingdom, however, were somewhat disappointing. In one of them, the comparison between albuterol, ipratropium bromide, and a placebo in children with bronchiolitis showed improved breathing with the first drug (77). However, a double-blind trial with albuterol failed to elicit any beneficial clinical effects and its use in

bronchiolitis was not advised by the authors (78). More recent papers still offer controversial opinions about the relevant actions of bronchodilators in bronchiolitis.

In a double-blind study Wang et al. (79) compared albuterol and ipratropium bromide in hospitalized patients between 2 months and 2 years of age who had failed to respond well to albuterol in the emergency room. Although improvement in oxygen saturation in children who received both drugs was observed, between them statistical significant advantage could not be demonstrated, nor was there any difference in clinical parameters with the control group. The more positive results related by Schuh et al. may be due to the less severe symptoms presented by his group.

Early bronchodilator administration was also recommended by another study that showed clinical and laboratory (pulse oximeter) improvement (80). It has been suggested that individual factors determine the response of bronchodilators in RSV-infected infants (81).

Sly et al. (82), analyzing pulmonary function tests of infants under 6 months in the convalescent phase of bronchiolitis, found no major influence on the maximum volume of oxygenation after the administration of albuterol. The disparity of findings between clinical and physiopathological studies may occur because the use of chloral hydrate for sedation prior to administering pulmonary function tests can influence the final results. This drug interferes with the pharmacological action of albuterol. Moreover, the clinical improvement could be observed during a certain treatment period, not after a single dose.

Welliver et al. (13) admitted that a small number of infants and toddlers benefited from the use of bronchodilators in lower respiratory tract infections associated with wheezing without significant adverse reactions, even though it was not feasible to detect improvement by clinical judgement. He also emphasized that critically ill children should receive bronchodilators only with oxygen supplementation.

Other studies have indicated that nebulized racemic adrenaline was more effective than a placebo (83) or albuterol (84) in treating infant bronchiolitis.

## **b) Ribavirin**

The first trials with this antiviral drug began in 1981, and it has been available for use in the United States since 1986. Until now, only eight controlled studies have been published in English. Its use is also controversial, especially considering the high cost of the drug, whose cost-benefit has been evaluated (11, 21, 85), as well as its administration using aerosol and its potential toxicity to persons exposed.

Ribavirin is a nucleotide whose main action is in RNA expression, inhibiting viral protein synthesis (65). It produced improvement in arterial oxygenation in previously healthy infants with underlying severe respiratory disease (86).

For practical purposes, the drug should be given in a chamber or tent with an appropriate nebulizer that generates microparticles of 2  $\mu\text{m}$  for a prolonged period, 18-20 hours per day for 5 days (85). Its use should be avoided in children with severe bronchiolitis requiring

mechanical ventilation because of the deposit the drug leaves on the ventilator circuit, unless special technical adaptations are made.

Despite this impediment, Smith et al. (87) were able to hasten hospital discharge by using ribavirin in mechanically ventilated patients. Drug utilization is advised within the first 28 hours of hospitalization in patients whose clinical features have endured 4 or 5 days. However, reduced hospitalizations were not achieved in patients receiving early ribavirin administration, compared to a control group in another study (85).

The majority of authors advise the use of ribavirin in special situations: patients who are not severely ill and are early in their course, but have potential risk factors or preexisting diseases, such as prematurity, under 6 weeks of age, or present pulmonary or cardiac abnormalities (namely bronchopulmonary dysplasia, congenital heart disease with pulmonary hypertension), immunodeficiencies, or are severely affected by  $pO_2$  under 65 mm Hg or have  $CO_2$  retention (11, 21, 65, 86, 88).

### VIII. SEQUELAE

Follow-up may reveal persistent symptoms in the early weeks or months following bronchiolitis. In his study with Brazilian children, Fischer reported that 77% suffered from at least one episode of wheezing and 22% had to be readmitted to the hospital within 60 days of discharge. Several authors have highlighted the link between bronchiolitis and asthma. Others deny this association, even in atopic cases or with positive family history for asthma (89, 90). There are some clues that lung abnormalities may persist for years following apparent clinical recovery, even in children who remain symptom-free (3).

The conflicting results given by follow-up studies may be due to varying criteria for the selection of indexed cases, absence of control groups, inclusion of children presenting multiple variables, such as environmental factors, atopic predisposition, previous respiratory infections, and other aspects that enhance the controversy around this subject (71, 91).

Martinez et al. (92) have an interesting observation on the occurrence of respiratory symptoms after bronchiolitis. They prospectively measured airway conductance before and after infectious episodes. They then concluded that infants with smaller conductance values had a greater risk of developing subsequent wheezing, suggesting that this functional abnormality is not a sequel of bronchiolitis, but a predisposing factor for exacerbation of the symptoms.

The condition, known as bronchiolitis obliterans, consists of anatomopathological sequelae of many attacks to the small airways, such as gas and lipid inhalation (lipoid pneumonia) or even autoimmune diseases. It rarely occurs in childhood and should not be considered a complication of RSV infection (3). It can follow adenovirus, influenza, or measles infections. The histologic lesion consists of cellular agglomerate including fibroblasts, leukocytes, and fibrin that partially or completely obstruct the airway lumen, thereby leading to atelectasis and other complications, such as bronchiectasis and unilateral hyperlucent lung syndrome, as described by McLeod and Swyer-James (93, 94).

## IX. PREVENTION

RSV is present in copious amounts in the secretions of the respiratory tract of symptomatic persons infected with the virus and is communicable directly through the large droplets of these secretions or indirectly through RSV-contaminated hands or fomites. There have been reports of life-threatening bronchiolitis or pneumonia in children with heart, lung, or immune system disorders. Measures should be taken to control nosocomial transmission, particularly in high-risk individuals. The precautions required for limiting the incidence of nosocomial RSV infections are strict hand washing and use of gloves and robes (3, 95).

Hyperimmune gammaglobulin IV, although not yet approved by the Blood Products Advisory Committee of the U.S. Food and Drug Administration, was examined by the RSV Immune Globulin Study Group (96). The results of a multicenter clinical assay study appear to demonstrate the efficacy of intravenous administration of immune globulin in preventing lower respiratory tract infection in high-risk children who experienced increased titers of RSV antibodies. The group that had the highest dosages had the lowest number of lower respiratory infections, the fewest days hospitalized or in intensive care, and received the least ribavirin.

The formalin-inactivated vaccine employed in the 1960s failed to demonstrate efficacy with development of more severe diseases after exposure to the wild virus. Indeed, its use was disapproved (97).

Currently, new expectations in bronchiolitis prevention have been encouraged by experimental studies that assess immunity to RSV infection using vaccines with subunits of F and G glycoproteins. These glycoproteins are capable of inducing neutralizing antibodies, principally F, which appears to be the more important viral antigen in terms of cellular and humoral immunity induction. Efficacious RSV immunization may be achieved with the development of subunit vaccines consisting of F and G glycoproteins. Administration of purified F protein vaccines in adults and children over 2 has resulted in immunogenicity (75). Others are exploring the possibility of immunization with recombinant vaccinia viruses that have complementary DNA for the coding regions of RSV F and G glycoproteins inserted into the thymidine kinase region (97).

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**X. REFERENCES**

1. Morris JA, Blount RE Jr., Savage RE. *Recovery of a cytopathogenic agent from chimpanzees with coryza*. Proc Soc Exp Biol Med 1956;92:514.
2. Chanock R, Roizman B, Myers R. *Recovery from an infant with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization*. Am J Hyg 1957;66:281.
3. Wohl MEB. *Bronchiolitis*. In: Chernick V, ed. *Kendig's disorders of the respiratory tract in children*. 5th ed. Philadelphia, PA: Saunders; 1990.
4. McConnochie KM. *Bronchiolitis: What's in the name?* Am J Dis Child 1983;137:11.
5. Fischer GB, Mendonca PJC. *Bronquiolite viral aguda*. In: Ferreria O. *Pneumologia, cadernos de terapeutica*. 2a. ed. Rio de Janeiro: Cultura Médica; 1991.
6. Cherian T, Simoes EAF, Steinhoff MC, Chitra K, John M, Raghupathy P, John J. *Bronchiolitis in tropical South India*. Am J Dis Child 1990;144:1026-1030.
7. Korppi M, Koskela M, Jalonen E, Leinonen M. *Serologically indicated pneumococcal respiratory infection in children*. Scand J Infect Dis 1992;24:437-443.
8. Singh M, Singhi S. *Bronchiolitis-like presentation of Branhamella catarrhalis bronchopulmonary infection*. Indian Pediatr 1989;26:1044-1046.
9. McIntosh K. *Pathogenesis of severe acute respiratory infections in the developing world: Respiratory syncytial virus and parainfluenza viroses*. Rev Infect Dis 1991;13 (suppl 6):492-500.
10. Fischer GB. *Bronquiolite*. Tese de Doutorado em Pediatria. Porto Alegre, Brasil (dados nao publicados).
11. Shaw KN, Bell LM. *RSV bronchiolitis: The disease, distress and decisions*. Report on Pediatric Infectious Diseases no. 2, 1992.
12. Degré M. *Interaction between viral and bacterial infections in the respiratory tract*. Scand J Infect Dis. no. 2, 1992.
13. Welliver RC. *The therapeutic significance of the presence of wheezing in acute lower respiratory infection*. In: Gadomski A, ed. *Acute lower respiratory infection & child survival in developing countries*. Workshop. Washington, DC; 1989.
14. Chattopadhyaya D, Chatterjee R, Anand VK, Kumari S, Patwari AK. *Lower respiratory tract infection in hospitalized children due to respiratory syncytial (RS) virus during a suspected epidemic period of RS virus in Delhi*. J Trop Pediatr 1992;38:68-73.
15. Dawson KP, Mogridge N. *Acute bronchiolitis: A three-year study*. N Z Med J 1989;11:102:528-529.
16. Sant'Anna CC, Cunha AJL, Dalcolmo M. *Infecções respiratórias agudas na criança*. Rio de Janeiro: Cultura Medica; 1989.
17. Nascimento JP, Siqueira MM, Suttmoller F, Krawczuk MM, Farias V, Ferreira V, Rodrigues JJ. *Longitudinal study of acute respiratory diseases in Rio de Janeiro: Occurrence of respiratory viruses during four consecutive years*. Rev Inst Med Trop Sao Paulo 1991;33:287-296.

18. Nwankwo MU, Dym AM, Schuit KE, Offor E, Omene JA. *Seasonal variation in respiratory syncytial virus infections in children in Benin City, Nigeria*. Trop Geogr Med 1988;40:309-313.
19. Wang GD. *An outbreak of epidemic bronchiolitis*. Chung Hua Liu Hsing Ping Hsueh Tsa Chih 1990;11:198-201.
20. Holberg CJ, Wright AL, Martinez FD, Ray CG, Taussig LM, Lebowitz MD. *Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life*. Am J Epidemiol 1991;133:1135-1151.
21. Hall B, McBride JT. *Respiratory syncytial virus: From chimps with colds to conundrums and cures*. N Engl J Med 1991;325:57-58.
22. Carlsen K, Larsen S, Bjerve O, Leegard J. *Predisposing factors and characterization of infants at risk*. Pediatr Pulmonol 1987;3:153-160.
23. McConnochie KM, Roghmann KJ. *Parental smoking, presence of older siblings and family history of asthma increase risk of bronchiolitis*. Am J Dis Child 1986;140:806-818.
24. Pullan CR, Toms GL, Martin AJ, Garden PS, Webb JKG, Appleton DK. *Breastfeeding and respiratory syncytial virus infections*. Br Med J 1980;2281:1034-1036.
25. Morris K, Morgenlander M, Coulehan JL, Gahagen S, Arena VC, Morganlander M. *Wood-burning stoves and lower respiratory tract infections in American Indian children*. Am J Dis Child 1990;144:105-108.
26. Benigno V, Varia F, Cusimano RA, Ziino Colanino G, Basile A, La Grutta S. *Recurrent wheezing in subjects with preceding bronchiolitis. Role of environmental and genetic factors*. Pediatr Med Chir 1991;13:255-258.
27. McConnochie KM, Roghmann KJ. *Wheezing at 8 and 13 years: Changing importance of bronchiolitis and passive smoking*. Pediatr Pulmonol 1989;6:138-146.
28. Van Steensel-Moll HA, Van de Voort E, Bos AP, Rotoherbth PH, Neijens HJ. *Respiratory syncytial virus infections in children admitted to the intensive care unit*. Pediatrie 1989;44:583-588.
29. Carballal G, Siminovich M, Murtagh P, Cerqueiro MC, Avila M, Salomon H, Catalano M, Weissenbacher M. *Etiological, clinical and pathological analysis of 31 fatal cases of acute respiratory tract infections in Argentinian children less than five years of age*. Rev Infect Dis 1990;12 (Suppl 8):1074-1080.
30. MacDonald NE, Hall CB, Suffin SC, Alexon C, Harris PJ, Manning JA. *Respiratory syncytial viral infection in infants with congenital heart disease*. N Engl J Med 1982;307:397-400.
31. Tammela OKT. *First year infections after initial hospitalization in low birth weight infants with and without bronchopulmonary dysplasia*. Scand J Infect Dis 1992;24:515-524.
32. Couvreur J. *Bronchopneumopathies virales*. In: Gerbeaux J, Couvreur J, Tournier G. Pathologie respiratoire de l'enfant. 2a ed. Paris: Flammarion; 1979.
33. Smith JJ, Lemen RJ, Tausig LM. *Mechanisms of viral induced lower airway obstruction*. Pediatr Infect Dis J 1987;6:837-842.

34. Gardner PS, McQuillin J, Court SDM. *Speculation on pathogenesis in death from respiratory syncytial virus infection*. Br Med J 1970;1:327-330.
35. Casale TB. *Neuropeptides and the lung*. J Allergy Clin Immunol 1991;88:1-14.
36. Welliver RC, Wong DT, Sun M. *The development of respiratory syncytial virus specific IgE and the release of histamine in nasopharyngeal secretions after infection*. N Engl J Med 1981;305:841-846.
37. Bui RHD, Molinaro GA, Kettering JD, Heiner DC, Imagawa DT, Geme JWS. *Virus specific IgE and IgG4 antibodies in serum of children infected with respiratory syncytial virus*. J Pediatr 1987;101:889-896.
38. Santangelo G, Giannotti G, Amato C. *Studio quantitativo delle sottopopolazioni T nei soggetti affetti da bronchiolite*. Boll Ist Sieroter Milan 1988;2:156-158.
39. Welliver RC, Kaul A, Ogra PL. *Cell-mediated immune response to respiratory syncytial virus infection. Relationship to the development of reactive airway disease*. J Pediatr 1979;3:370-375.
40. Scott R, Kaul A, Scott M, Chiba Y, Ogra PL. *Development of in vitro correlates of cell-mediated immunity to respiratory syncytial virus infections in humans*. J Infect Dis 1978;6:810-817.
41. Mito K, Chiba Y, Suga K, Nakao T. *Cellular immune response to infection with respiratory syncytial virus and influence of breast-feeding on response*. J Med Virol 1984;14:323-332.
42. Bertotto A, Stagni G, Sonaglia F, Caprino D, Vaccaro R. *Serum migration-inhibitory activity in infants with respiratory syncytial virus bronchiolitis*. Boll Inst Sieroter Milan 1981;2:150-154.
43. Kim HW, Leikim SL, Arrobio J, Brandt CD, Chanock RM, Parrott RH. *Cell-mediated immunity to respiratory syncytial virus induced by inactivated vaccine or by infection*. Pediatr Res 1976;10:75-78.
44. Kapikian AZ, Mitchell RH, Chanock RM, Shvedoff RA, Stewart CE. *An epidemiological study of altered clinical reactivity to respiratory syncytial virus infection in children previously vaccinated with an inactivated RS virus vaccine*. Am J Epidemiol 1969;89:405-421.
45. Neligan GA, Steiner H, Gardner PS, McQuillin J. *Respiratory syncytial virus infection of the newborn*. Br Med J 1970;3:146-147.
46. Lamprecht CL, Krause HE, Mufson MA. *Role of maternal antibody in pneumonia and bronchiolitis due to respiratory syncytial virus*. J Infect Dis 1976;3:211-217.
47. Bruhn FW, Yeager AS. *Respiratory syncytial virus in early infancy. Circulating antibody and severity of infection*. Am J Dis Child 1977;131:145-148.
48. Parrot RH, Kim KW, Arrobio JO, Hodes DS, Murphy BR, Brandt CD, Camargo E, Chanock RM. I. *Epidemiology of respiratory syncytial virus in Washington, DC. II. Infection and disease with respect to age, immunological status, race and sex*. Am J Epidemiol 1973;98:289-300.
49. Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL. *Risk of respiratory syncytial virus infection from low income families in relationship to age, sex, ethnic group and maternal antibody level*. J Pediatr 1981;5:708-715.
50. Santa Ana PPS, Arrobio JO, Kim HW, Brandt CD, Chanock RM, Parrot RH. *Serum complement in acute bronchiolitis*. Proc Soc Exp Biol Med 1970;134:499-503.

51. Henderson FW, Collier AM, Clyde Jr. WA, Denny FW. *Respiratory syncytial virus infections, reinfections and immunity: A prospective longitudinal study in young children.* N Engl J Med 1979;300:530-534.
52. Kaul TN, Welliver RC, Ogra PL, Wong DT, Udwardia RA, Riddlesberger K. *The secretory antibody response to respiratory syncytial virus infection.* Am J Dis Child 1981;135:1013-1016.
53. Kaul TN, Welliver RC, Ogra PL. *Development of antibody-dependent cell-mediated cytotoxicity in the respiratory tract after natural infection with respiratory syncytial virus.* Infect Immun 1982;37:492-498.
54. McIntosh K, Masters HB, Orr I, Chao RK, Barkin RM. *The immunologic response to infection with respiratory syncytial virus in infants.* J Infect Dis 1978;1:24-32.
55. Laing I, Friedel F, Yap PLL, Simpson H. *Atopy predisposing to acute bronchiolitis during an epidemic of respiratory syncytial virus.* Br Med J 1982;284:1070-1072.
56. McConnochie KM, Roghmann KJ. *Bronchiolitis as a possible cause of wheezing in childhood: New evidence.* Pediatrics 1984;74:1-10.
57. Carlsen KH, Larsen S, Orstavik I. *Acute bronchiolitis in infancy: The relationship to later recurrent obstructive airways disease.* Eur J Resp Dis 1987;70:86-92.
58. Hall CB, Hall WJ, Speers DM. *Clinical and physiological manifestations of bronchiolitis and pneumonia.* Am J Dis Child 1979;133:798-802.
59. Shaw KN, Bell LM, Sherman NH. *Outpatient assessment of infants with bronchiolitis.* Am J Dis Child 1991;145:151-154.
60. Menahem S. *Respiratory syncytial virus and supraventricular tachycardia in an infant.* Int J Cardiol 1991;32:249-251.
61. Gozal D, Colin AA, Jaffe M, Hochberg Z. *Water, electrolyte and endocrine homeostasis in infants with bronchiolitis.* Pediatr Res 1990;27:204-209.
62. Perrin C, Charbonneau P, Petiot JE, Freymuth E, Buthiau E, Lehouezec. *Indice predictif de gravité des bronchiolites à virus respiratoire syncytial du nourrisson.* Ann Pediatr (Paris) 1986;33:401-406.
63. Dawson KP, Long A, Kennedy J, Mogridge N. *The chest radiograph in acute bronchiolitis.* J Paediatr Child Health 1990;26:209-211.
64. Friis B, Eiken M, Hornsleth A, Jensen A. *Chest X-ray appearances in pneumonia and bronchiolitis. Correlation to virological diagnosis and secretory bacterial findings.* Acta Paediatr Scand 1990;79:219-225.
65. American Academy of Pediatrics Committee on Infectious Diseases. *Ribavirin therapy of respiratory syncytial virus.* Pediatrics 1987;79:475-478.
66. Organización Panamericana de la Salud. *Infecciones respiratorias agudas en los niños.* Publ. Cient. No. 493. Washington, DC; 1985.
67. Ho L, Collins G, Landau LI, Le Souef PN. *Effect of salbutamol on oxygen saturation in bronchiolitis.* Arch Dis Child 1991;66:1061-1064.

68. Oggero R, Ricca V, Parisi E, Guardamagna O, Celestino D, Cambursano P, Negro F. *Il punteggio clinico per la diagnosi de bronchiolite nell'età del lattante*. Min Ped 1983;35:89-92.
69. Jacobs JW, Peacock DB. *Differentiation of actively and passively acquired complement-fixing antibodies in infants with respiratory syncytial virus infection*. J Med Microbiol 1970;3:313-324.
70. Sibbald B, Hord MEC, Gregg I. *A family study of the genetic basis of asthma and wheezy bronchitis*. Arch Dis Child 1980;55:354-357.
71. Simpson H, Mok JYK. *Outcome of respiratory disease in childhood*. In: Milner AD, Martin RJ. Neonatal and pediatric respiratory medicine. London: Butterworths; 1985.
72. Brasil, Ministerio de Salud. *Manual de normas para asistencia e controle das infecções respiratorias agudas na infancia*. 3a. ed., Brasília, DE. (No prelo).
73. Carlsen KH, Leegaard J, Larsen S, Orstavik I. *Nebulized beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis*. Arch Dis Child 1988;63:1428-1433.
74. Milner AD, Murray M. *Acute bronchiolitis in infancy: Treatment and prognosis*. Thorax 1989;44:1-5.
75. Chanock RM, Parrot RH, Connors M, Collins PL, Murphy BR. *Serious respiratory tract disease caused by respiratory syncytial virus: Prospects for improved therapy and effective immunization*. Pediatrics 1992;90:137-143.
76. Schuh S, Cann G, Reisman JJ, Kerem E, Benfur L, Petric M, Levison H. *Nebulized albuterol in acute bronchiolitis*. J Pediatr 1990;117:633-637.
77. Stokes GM, Milner AD, Hodges IGC, Henry RL, Elphick MC. *Nebulized therapy in acute severe bronchiolitis*. Arch Dis Child 1983;58:279-283.
78. Henry RL, Milner AD, Stokes GM. *Ineffectiveness of ipratropium bromide in acute bronchiolitis*. Arch Dis Child 1983;925:926.
79. Wang EE, Milner R, Allen U, Maj H. *Bronchodilators for treatment of mild bronchiolitis: A factorial randomized trial*. Arch Dis Child 1992;67:289-293.
80. Klassen TP, Rowe PC, Sutcliffe T, Ropp LJ, McDowell IW, Li MM. *Randomized trial of salbutamol in acute bronchiolitis*. J Pediatr 1991;119:807-811.
81. Soto ME, Sly PD, Urne E, Taussig LM, Landau LI. *Bronchodilator response during acute viral bronchiolitis in infancy*. Pediatr Pulmonol 1985;2:85-90.
82. Sly PD, Lanteri CJ, Raven JM. *Do wheezy infants recovering from bronchiolitis respond to inhaled salbutamol?* Pediatr Pulmonol 1991;10:36-39.
83. Kristjansson S, Carlsen L, Wennergen G, Stannegard IC, Carlsen KH. *Nebulized racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers*. Arch Dis Child 1993;69:650-654.
84. Sánchez I, De Koster J, Powell RE, Wolstein R, Chernick V. *Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis*. J Pediatr 1993;122:145-151.

85. Groothuis JR, Woodin KA, Katz R, Robertson AD, McBride JT, Hal CB, McWilliams BC, Lauer BA. *Early ribavirin treatment of respiratory syncytial viral infection in high-risk children.* J Pediatr 1990;117:792-798.
86. Turner RB. *Ribavirin for respiratory syncytial virus infections.* Res Pediatr Infect Dis 1994;4:36.
87. Smith DW, Frankel LR, Mathers LH, Tang ATS, Ariagno RL, Prober CG. *A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection.* N Engl J Med 1991;325:24-29.
88. Taber LH, Knight V, Gilbert BE, McClung HW, Wilson SZ, Norton J, Turson JM, Gordon WH, Atmar RL, Schlaudt WR. *Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants.* Pediatrics 1983;72:613-618.
89. Mok JYK, Simpson H. *Symptoms atopy and bronchial reactivity after lower respiratory infection in infancy.* Arch Dis Child 1984;59:299-305.
90. Pullan CR, Hey EN. *Wheezing, asthma and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy.* Br Med J 1982;284:1665-1669.
91. Caswell SJ, Thompson AH, Ashmore SP, Beardsmore CS, Simpson H. *Latent sensitization to respiratory syncytial virus during acute bronchiolitis and lung function after recovery.* Arch Dis Child 1990;65:946-952.
92. Martinez FD, Morgan WJ, Wright AL, Holberg CJ, Taussig LM. *Diminished lung function as a predisposing factor for wheezing respiratory illness in infants.* N Engl J Med 1988;319:1112-1117.
93. Hardy KA, Schidlow DV, Zaeri N. *Obliterative bronchiolitis in children.* Chest 1988;93:460-466.
94. Labbe A, Dechelotte P, Creveaux I, Poitrineau P, Gaulme J. *Bronchiolite folliculaire: Une observation pediatrique.* Rev Mal Resp 1992;9:324-326.
95. Tablan OC, Anderson LJ, Arden NH, Breiman RF, Butler JC, Neil MN. *Guidelines for prevention of nosocomial pneumonia.* Infect Control Hosp Epidemiol 1994;15:588-627.
96. Groothuis JR, Simoes EAF, Levin MJ, et al. *Prophylactic administration of respiratory syncytial virus immune globulin to high risk infants and young children.* N Engl J Med 1993;329:1524-1530.
97. Steinhoff MC. *Viral vaccines for the prevention of childhood pneumonia in developing nations: Priorities and prospects.* Rev Infect Dis 1991;13 (Suppl):562-570.

