

## ETIOLOGY, EPIDEMIOLOGY, CLINICAL IMPLICATIONS AND TREATMENT OF ACUTE BRONCHIOLITIS - A REVIEW OF THE LITERATURE

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### Abstract

Bronchiolitis is an acute viral infection that is one of the leading causes for hospitalization in young children. Despite the fact that etiology and clinical signs of the disease are well-known, in this article we will give summary of the latest scientific data related to the bronchiolitis. Bronchiolitis still remains an active field for research with many open questions still remains to be answered – ista recenica. Majority of bronchiolitis episodes are caused by respiratory syncytial virus and most often occur in children aged between two and 24 months. Most children get better with supportive care at home. A small number of children require hospitalization and treatment with oxygen and hydration.

**Key words:** bronchiolitis, RSV, bronchodilators, corticosteroids, ribavirin

Bronchiolitis is an acute respiratory illness precipitated by a viral infection resulting in obstruction of the small airways. While mortality due to bronchiolitis is low in developed countries, it remains an important illness because of the frequency with which infants require hospitalization and because of the potential association with asthma during later life [1].

Although the term “bronchiolitis” refers to inflammation of the bronchioles, these findings are rarely observed directly but inferred in a young child who presents with respiratory distress in association with signs of a viral infection [2]. Definitions of bronchiolitis vary and may account for some of the variability in the clinical evidence derived from published studies [2]. Bronchiolitis of infancy is a clinically diagnosed respiratory condition presenting with breathing difficulties, cough, poor feeding, irritability, and in the very young, apnoea. These clinical features, together with wheeze and/or crepitations on auscultation combine to make the diagnosis [3]. Clinical definitions of acute viral bronchiolitis vary between countries. While in many countries including the USA wheezing is fundamental for the diagnosis, in the U.K., Australia and New Zealand wheezing is not an obligatory diagnostic criterion [4].

The initial abnormalities of the lower respiratory tract in respiratory syncytial virus (RSV) bronchiolitis are necrosis of the respiratory epithelium and destruction of the ciliated epithelial cells which occurs within 24 hours of acquisition of infection, followed by peribronchiolar infiltration with lymphocytes. The submucosa becomes edematous, but there is no destruction of collagen or elastic tissue [5].

Bronchiolitis is an active area of research, and many important studies have advanced the understanding of this disorder in the past few years [2]. The aim of this review is to give summary on the scientific evidence related to bronchiolitis.

### Etiology

The number of viruses recognized to cause bronchiolitis has markedly expanded with the availability

of sensitive diagnostic tests that use molecular amplification techniques [2]. The majority of bronchiolitis episodes are caused by respiratory syncytial virus (RSV), with estimates ranging for 50% to 90% of cases [5]. Other causes include the parainfluenza viruses, primarily parainfluenza virus type 3, influenza and human metapneumovirus, rhinovirus and adenovirus [2, 5]. The clinical courses of RSV and human metapneumovirus seem to be similar; most children are infected during annual widespread wintertime epidemics, with a subset developing bronchiolitis [2, 5].

RSV is an enveloped, single-stranded RNA virus. There is antigenic variation among the RSV strains, and monoclonal antibodies have made it possible to divide RSV isolates into two major groups (A and B) and into subtypes within each group. The severity of infection may vary with subgroup; RSV A infections generally are more severe [6].

The parainfluenza viruses are the second most common cause of bronchiolitis and are responsible for autumn and spring epidemics, usually preceding and following the RSV outbreak [1]. Rhinovirus, and *Mycoplasma pneumoniae* are responsible for an increasing number of cases of wheezing-associated respiratory illness with increasing age, but RSV and the parainfluenza viruses have been shown to provoke wheezing at all ages [1].

Human metapneumovirus (hMPV) is a respiratory viral pathogen that causes a spectrum of illnesses that range from asymptomatic infection to severe bronchiolitis. In 2001, van den Hoogen et al described the identification of this new human viral pathogen from respiratory samples submitted for viral culture during the winter season [7]. Human metapneumovirus is thought to cause 4-12% of bronchiolitis episodes worldwide, although its prevalence differs from country to country [5]. Human metapneumovirus has been estimated to account for 3% to 19% of bronchiolitis cases [8].

According to Baccala et al RSV was identified in about 70% of hospitalized infants with bronchiolitis during seasonal winter epidemics, followed by human metapneumovirus in about 3-19% or rhinoviruses (about

20%). Other respiratory viruses have also been reported, indicating significant causes of bronchiolitis and hospitalization during seasonal epidemics [9].

In the study conducted by Hall et al among 5067 children enrolled in the study, 919 (18%) were infected with RSV, 564 (61%) were hospitalized and 355 were outpatients. Among 564 inpatients with RSV infection, bronchiolitis was diagnosed in 397 (70%) [10].

In the study of Semple et al during the 4-month 2001–2002 winter season, 196 infants with bronchiolitis who were eligible for the study were admitted to the hospital. RSV was detected in samples from 174 (89%) of 196 infants with bronchiolitis [11].

Boivin et al evaluated the percentage of hospitalizations for acute respiratory tract infections in children <3 years of age in a prospective study during winter and spring of 2002. hMPV was detected in 12 (6%) of the 208 children hospitalized for acute respiratory tract infections, RSV in 118 (57%), and influenza A in 49 (24%). Bronchiolitis was diagnosed in 8 (68%) of HMPV infected children; of those with RSV infection, bronchiolitis was diagnosed in 99 (84%) and bronchiolitis was found in 51% of children infected with influenza A [12].

Approximately 75%–85% of cases of bronchiolitis can be attributed to infection by human respiratory syncytial virus, and 10%–20% can be attributed to infection by rhinovirus or parainfluenza virus. Rarely, human influenza virus, adenovirus, and *Bordetella pertussis* are detected. In 10% of cases, no pathogen is detected. Human metapneumovirus is now recognized as one of several viral pathogens that can cause bronchiolitis in the absence of other pathogens. Preliminary epidemiological data have described a prevalence of 1.5%–8% for hMPV infection in children with respiratory tract infections who were admitted to the hospital in Australia and France [13, 14].

**Dual infections:** Molecular diagnostic techniques have also revealed that young children with bronchiolitis and other acute respiratory illnesses are often infected with more than 1 virus. Rates of coinfection have ranged from 10% to 30% in samples of hospitalized children, most commonly with RSV and either hMPV or rhinovirus [2]. A recent large prospective study of children younger than 5 years of age hospitalized with RSV infection revealed a coinfection rate of 6%. In 58 of the samples (6%), coinfecting viruses were identified, including 26 samples with influenza virus, 8 with parainfluenza virus, 11 with rhinovirus, 6 with adenovirus, 5 with cytomegalovirus, and 4 with other viruses [10]. Whether concomitant infection increases the severity of bronchiolitis is controversial [2]. Dual infection with HMPV and RSV confers increase in relative risk of admission to a pediatric intensive-care unit for mechanical ventilation [2]. Semple et al detected coinfection with human metapneumovirus in 70% of infants with RSV bronchiolitis sufficiently severe to require admission to the pediatric intensive-care unit for ventilatory support [11]. This high rate of coinfection raises the possibility that coinfection with RSV and human metapneumovirus might be another determinant of RSV disease severity. Indeed, of 10 studied

infants with severe RSV bronchiolitis and no other risk factors for severe disease, 9 (90%) were coinfecting with human metapneumovirus [8]. Other studies, however, have revealed no increased illness severity associated with the presence of more than 1 virus. Caracciolo et al found that hMPV/RSV coinfections were common events (19 of 39; 48.7%), but no differences in disease severity (gauged by duration of hospitalization and requirement of oxygen) were observed [15].

### Epidemiology

Bronchiolitis is an extremely common disease. It occurs most often in children aged between two and 24 months, with peak infection occurring between three and six months of age. About 25% of infants have bronchiolitis during their first year, and 95% have had the disease by their second birthday [5].

Serious cases of bronchiolitis occur most commonly in infants younger than 1 year, particularly in the 1- to 3-month age span. Bronchiolitis is observed more commonly in infants from families of low socioeconomic status, in infants raised in crowded living conditions, in infants passively exposed to cigarette smoke within the home, and in infants who have not been breastfed [1]. In a prospective case-control study of infants born at 33–35 weeks gestation or who were less than six months of age at the start of the RSV season, breast feeding for more than two months had a protective effect [16]. Boys have more severe disease and a higher incidence of hospitalization [6]. Children whose cardiorespiratory or immune function is compromised are at increased risk of severe disease due to RSV infection [5].

Bronchiolitis is seen frequently in all geographic areas. It is a highly seasonal disease—comparatively few cases occur during the summer months, and activity peaks during the winter months. In the northern hemisphere, bronchiolitis occurs most frequently in mid-December and mid-March; in the southern hemisphere, most cases are seen during the winter months of July and August. In tropical climates, where cold weather does not occur, bronchiolitis is seen most commonly during the rainy seasons, when crowding occurs as a result of populations being driven indoors [1].

Children who are older than two years typically do not develop bronchiolitis, but can be infected with RSV. It usually causes symptoms similar to those of the common cold or mild wheezing and at times the illness is significant enough to require evaluation by a health care provider [6].

Epidemiologic study results of bronchiolitis have suggested a high degree of morbidity but low mortality. More than one third of children develop bronchiolitis during the first 2 years of life; of these approximately 1 in 10 will be hospitalized. Although the number of hospitalizations seems to have increased, the mortality rate is low; fewer than 400 deaths related to RSV occur annually. Most deaths that result from bronchiolitis occur in infants during the first 6 months of life; infants with prematurity and underlying cardiopulmonary disease or immunodeficiency are at higher risk [2].

From 2000 through 2004, the average annual rate of RSV-associated hospitalization was 3 per 1000 children under the age of 5 years and 17 per 1000 children under the age of 6 months. Among 564 inpatients with RSV infection, bronchiolitis was diagnosed in 397 (70%) [10].

Around 3% of all infants younger than one year are admitted to hospital with bronchiolitis. Based on Scottish morbidity recording for the years 2001 to 2003 a mean of 1,976 children per year (aged up to 12 months) were admitted to hospital with bronchiolitis as the principal diagnosis. The rate of admissions to hospital with bronchiolitis has increased over the past 10 years. The reasons for this are not fully understood and are likely to be multifactorial and include improved survival of preterm infants [17].

### **RSV bronchiolitis and environment**

Tobacco smoke contains approximately 4,000 toxic chemicals, including oxidative gases, heavy metals, cyanide, and at least 50 carcinogens. Passive exposure to tobacco smoke significantly contributes to morbidity and mortality in children. Children, in particular, seem to be the most susceptible population to the harmful effects of environmental tobacco smoke. Children are exposed to tobacco smoke not only in their homes but also in schools, restaurants, child-care settings, cars, buses, and other public places. The home is the greatest single source of environmental tobacco smoke for children. Paternal smoking inside the home leads to significant maternal and fetal exposure to environmental tobacco smoke and may subsequently affect fetal health [18].

Given the impact that RSV bronchiolitis has on infants and the risks associated with this disease, it is important to try to understand those factors that may contribute to the severity of such an infection [19]. Tobacco smoke is the most common and important indoor environmental pollutant to which young children are exposed. The epidemiological association between parental smoking and acute lower respiratory illness in children is recognized [20]. Passive smoking was recognized as a cause of lower respiratory infection in children in the US Surgeon General report of 2006 and also in the UK Government SCOTH report [21, 22]. We identified 60 studies suitable for inclusion in the meta-analysis. Smoking by either parent or other household members significantly increased the risk of lower respiratory infections (LRI); odds ratios were 1.22 for paternal smoking, 1.62 if both parents smoked, and 1.54 for any household member smoking. Prenatal maternal smoking had a weaker effect than postnatal smoking. The strongest effect was on bronchiolitis, where the risk of any household smoking was increased by a 2.51 [23].

Maternal smoking exposure has been shown to reduce lung function in children, and several studies suggest that this effect on lung function is attributable primarily to exposure during pregnancy (intrauterine cigarette smoke exposure). Maternal smoking during pregnancy may impair in utero airway development or alter lung elastic properties. In addition, intrauterine smoking exposure may increase the risk for the development of

asthma; however, postnatal smoking exposure is considered to induce wheezing in children with asthma. Furthermore, Singh et al demonstrated in an animal model that intrauterine cigarette smoke exposure decreased cyclic adenosine monophosphate levels and increased phosphodiesterase-4 enzymatic activity, resulting in increased airway hyperresponsiveness, which may explain the potential mechanism by which intrauterine smoke exposure decreases lung function and leads to the development of asthma [19].

Lanari et al demonstrated that exposure to cigarette smoke, in general, seems to worsen the severity of the bronchiolitis [24]. Moreover, a study by Gurkan et al, in which cotinine levels were measured at index of hospitalization, showed that infants admitted to the hospital with severe RSV bronchiolitis were exposed more recently to cigarette smoke than infants hospitalized for non-respiratory diseases [25].

Passive smoking in the family home is a major influence on the risk of LRI in infants, and especially on bronchiolitis. Risk is particularly strong in relation to postnatal maternal smoking. Strategies to prevent passive smoke exposure in young children are an urgent public and child health priority [23].

### **RSV bronchiolitis and post-bronchiolitic wheeze and asthma**

Acute viral bronchiolitis is one of the most common causes of hospitalization during infancy. Wheezing is common in infants and young children who suffer from lower respiratory infections caused by different viruses, such as respiratory syncytial virus, rhinovirus, etc. There is some evidence that early-life RSV bronchiolitis may predispose some infants to the development of childhood asthma. One of the major questions regarding long-term side effects of bronchiolitis by respiratory syncytial virus is whether or not it induces asthma in later life [26].

Sigurs et al found that RSV bronchiolitis in infancy was strongly associated both with asthma as well as with other forms of bronchial obstructive disease and allergic sensitization at age 7 ½. There was no tendency for the frequencies of asthma and sensitization among the control children to catch up with those in the RSV group. The fact that RSV bronchiolitis had a substantially higher risk ratio for future asthma than a family history of atopy/asthma and also a significantly elevated risk ratio for allergic sensitization supports the theory that RSV may influence the mechanisms involved in the development of asthma and allergy in children [27].

Bont et al made an overview of relevant epidemiological studies analysing the relation between RSV bronchiolitis and airway morbidity. Wheezing episodes following RSV bronchiolitis were found in 42-71% of patients. Infants who will go on to have wheezing episodes will do so within 12-24 months after the first episode of RSV bronchiolitis. Less than 10% of children with recurrent wheezing following RSV bronchiolitis began to have wheezing episodes after they were 2 years old. It is generally assumed that wheezing episodes following

RSV bronchiolitis are associated with viral upper respiratory tract infections, and not allergen exposure in contrast to children who suffer allergic asthma. Both early and more recently published data indicate that airway morbidity following RSV bronchiolitis is transient and subsides during school age [28].

Kneyber et al recently published a meta-analysis confirming that wheezing is common after RSV bronchiolitis in infancy and may persist for 5 years of follow-up. Up to 5 years of follow-up after the RSV bronchiolitis, 40% of children reported wheezing, compared with only 11% in the control group. Between 5 to 10 years of follow-up, 22% of the bronchiolitis group reported wheezing, compared with 10% of the control group. The incidence of recurrent wheezing as defined by 3 wheezing episodes, also decreased with increasing years of follow-up, and 5 years of follow-up the difference between RSV and control groups was no longer significant. Regarding personal history of atopy, a family history of atopy and/or asthma, no significant differences between the RSV bronchiolitis and the control group were found. Therefore it seems unlikely that RSV bronchiolitis is a cause of atopic asthma in later life [29].

At present no study has convincingly identified any treatment strategy that can reliably prevent post-bronchiolitic wheezing [30]. Several placebo controlled trials studied the benefit of corticosteroid treatment on the development of subsequent wheezing. These studies have addressed the question whether corticosteroid treatment can influence the degree of respiratory sequel after RSV bronchiolitis. The results are not consistent, although most follow-up studies conducted by Richter, Bulow, and de Boeck report negative results [31, 32, 33]. A few studies report positive long-term effects on postbronchiolitic wheezing after corticosteroid treatment. Kajosaari et al recently reported results indicating that inhaled corticosteroid treatment during and after the acute phase of RSV bronchiolitis in infancy may have a beneficial effect on subsequent bronchial wheezing [34]. In addition, a study from Hesselmar et al presents results indicating that inhalation of corticosteroids for 6–8 weeks may reduce subsequent asthma and severe respiratory morbidity in infants hospitalized for RSV infection [35]. In conclusion, the majority of prospective placebo controlled studies do not show any long-term beneficial effects of steroid treatment for RSV bronchiolitis [30].

### Treatment

It is well-recognized that supportive therapy remains the mainstay for the treatment of bronchiolitis and that there is little justification for most of the pharmacological agents traditionally administered to bronchiolitic children. The new paradigm of evidence-based medicine, together with increased cost-awareness, has driven many efforts to educate physicians and hospitals in the treatment of RSV bronchiolitis at home and in the hospital, since it has been repeatedly demonstrated that inappropriate or unnecessary medications are administered to infants with bronchiolitis [5].

Most children with acute viral bronchiolitis have a self-limiting mild disease and can be safely managed at home with careful attention to feeding and respiratory status. Management mainly consists of good supportive care, and most infants do not require specific measures. Criteria for referral and admission may vary between hospitals. Generally, the decision to admit an infant with bronchiolitis to the hospital is based on the age of the patient, the phase of illness, the presence of risk factors, the severity of respiratory distress, the ability to take oral fluids, and social and local circumstances. Clinical practice in the acute management of bronchiolitis varies widely even between centres in one country, and there is much controversy, confusion, and lack of evidence over the best treatment for this common, life-threatening condition [4].

The mainstay of treatment for RSV infection is supplemental oxygen and hydration. Supplemental oxygen is indicated if haemoglobin saturation falls persistently below 90% in previously healthy infants [6]. In this case, adequate supplemental oxygen should be used to maintain haemoglobin saturation at or above 90%. Oxygen may be discontinued if haemoglobin saturation is at or above 90% and the infant is feeding well and has minimal respiratory distress [4]. Oxygenation and adequacy of ventilation should be monitored through the use of pulse oximetry and blood gas measurements. Progressive hypercarbia, hypoxemia unresponsive to oxygen administration, and apnea are indications for assisted ventilation [6]. It is strongly recommended that clinicians should assess hydration and ability to take fluids orally. Frequent small feeds are often used but nasogastric or intravenous fluids may be required to maintain hydration [4]. While the effect of supplemental oxygen on recovery from bronchiolitis is not known, oxygen supplementation is the prime determinant of the length of hospitalisation for infants with acute viral bronchiolitis [2].

Treatment of bronchiolitis is an ever-controversial topic in paediatrics. Frequently used interventions, including bronchodilators and steroids, have failed to show consistent and clinically relevant effects in meta-analyses of randomized trials. Current practice guidelines recommend only supportive measures, given the absence of clear evidence for any other approach [36].

Many pharmacological agents commonly used in the treatment of asthma are also widely used in the management of bronchiolitis. The rationale for the treatment of bronchiolitis with bronchodilators is weak. Airway obstruction is mainly a result of mucus plugs and cellular debris from bronchial inflammation and epithelial necrosis. The contribution of airway smooth muscle constriction (which is treatable) to the airway obstruction is minor in most cases. Furthermore, the role of inhaled  $\beta$ -selective bronchodilators has been debated for many years, and it is now well established that they play a very minor role in the treatment of bronchiolitis. They produce only modest, short term improvements in clinical scores, but do not decrease the rate or duration of hospitalization [5].

Inhaled epinephrine is thought to be the better agent with which to treat airway obstruction in acute bronchiolitis, because epinephrine stimulates the  $\alpha$ -adrenoreceptor causing arteriolar vasoconstriction in the airway mucosa and subsequent reduction of bronchial mucosal oedema [37].

When comparing epinephrine with placebo, no differences were found for length of hospital stay but there is some indication that epinephrine is effective for reducing hospital admissions. Combined treatment with systemic glucocorticoids (dexamethasone) and epinephrine may significantly reduce admissions. There is insufficient evidence to support the use of epinephrine with or without steroids for the treatment of bronchiolitis among children admitted to the hospital [38].

Although numerous studies have explored the benefit of using nebulized epinephrine or corticosteroids alone to treat infants with bronchiolitis, the effectiveness of combining these medications is not well established. During treatment of acute bronchiolitis in infants, an unexpected synergism was found between epinephrine and dexamethasone. Combined therapy with epinephrine and dexamethasone, as compared with placebo, appeared to reduce the rate of hospital admission in the 7 days after study enrollment by 9 percentage points, with a relative risk reduction of 35%. It was also found an apparent benefit from combined therapy on the secondary outcomes: infants in this group were discharged earlier from medical care and resumed quiet breathing and normal feeding sooner than did those in the placebo group. In contrast, neither dexamethasone alone nor epinephrine alone had any effect on these outcomes [36].

Future research should further assess the efficacy, harms and applicability of combined therapy. There is variation in how physicians manage bronchiolitis, reflecting the absence of clear scientific evidence for any treatment approach.

Corticosteroids have also been favored as an acute treatment for infants hospitalized with acute viral bronchiolitis. This practice is more common in some parts of the world than in others. Anti-inflammatory drugs like glucocorticoids (for example, prednisolone or dexamethasone) have been used based on apparent similarities between bronchiolitis and asthma. The belief that corticosteroids can prevent or reduce the major pathology of inflammation and edema of the bronchiolar mucosa is tempting [4].

Various studies have failed to conclusively define a beneficial role for routine use of glucocorticoids in the treatment of infants with bronchiolitis. Absence of treatment effects was consistent throughout studies despite substantial heterogeneity regarding included populations, interventions, and outcomes [39, 40, 41].

Previous systematic reviews have not shown clear benefit of glucocorticoids for acute viral bronchiolitis, but their use remains considerable. Despite these findings several small studies conducted by *Schuh*, *Csonka*, *Garrison* suggest that use of systemic steroids early in the course of bronchiolitis may be effective in preventing the progression of inflammation or, at least, in

modifying the course, effectively reduced disease severity, length of hospital stay, and the duration of symptoms among children [42, 43, 44].

Ribavirin is a nucleoside analogue that interferes with viral protein synthesis and is the only therapeutic agent available to treat the infection [5]. The role of ribavirin in the treatment of acute bronchiolitis is controversial. It has been suggested that the use of ribavirin may be of benefit during the acute illness and may reduce subsequent recurrent respiratory morbidity [45]. According to Smith et al in infants who require mechanical ventilation because of severe RSV bronchiolitis, treatment with aerosolized ribavirin decreases the duration of mechanical ventilation, oxygen treatment and the hospital stay [46]. Although study of Smith et al suggested that aerosolized ribavirin may be useful, the results of other clinical studies reported no clinically important differences with the use of ribavirin [4, 5, 6, 45]. The agent is now little used because of its high cost and disappointing results from placebo controlled trials. A treatment must be cost-effective to be useful.

Cysteinyl leukotrienes are significantly increased in respiratory secretions from infants with acute viral bronchiolitis and remain so at short-term follow-up, suggesting a possible role of these substances in the pathogenesis of the disease [4]. Comparing montelukast, a specific cysteinyl leukotriene receptor antagonist, with placebo in infants with a first episode of bronchiolitis; treatment was given from hospital admission until discharge. Montelukast did not improve length of stay, clinical severity scores or cytokine levels in nasal lavage fluid [47]. It follows that montelukast should not be used in acute viral bronchiolitis [4, 5, 6, 47].

Palivizumab, a humanised monoclonal IgG1 antibody specifically directed to the RSV fusion protein has been shown to be efficacious in preventing serious RSV disease in high risk patients [5]. The current recommendation is that neither immunoglobulins nor RSV monoclonal antibodies should be used in acute viral bronchiolitis [4].

Bronchiolitis is an acute viral infection, so antibiotic therapy is not recommended in the treatment of acute bronchiolitis in infants. At present, it is recommended to limit the use of antibacterial medications to children with bronchiolitis who have specific indications of the coexistence of a bacterial infection [4].

Currently, there is no acceptable means of preventing RSV infection or bronchiolitis. Several vaccine candidates are being investigated. Meaningful use of these vaccines is at least several years away [1]. Also under investigation is the use of an intravenous immunoglobulin preparation with high titers of RSV neutralizing antibody. Frequent infusions of this compound may prevent RSV infection in infants at high risk for serious disease due to RSV [4]. Administration of RSV-IGIV reduced the incidence of hospitalization by 41% to 57% and decreased the total days of hospitalization due to RSV infection by 53% to 97%. These findings have been demonstrated for preterm infants who did and who

did not have bronchopulmonary dysplasia. These findings are very encouraging, but RSV-IGIV prophylaxis is costly and logistically demanding [6].

A higher vitamin D intake than currently recommended might be needed to offer protection against diseases such as acute lower respiratory infections. Increased vitamin D supplementation could have important public health consequences, as bronchiolitis and pneumonia are the most common reasons for hospitalization in young children [48].

Bronchiolitis still remains an active field for research with many open questions to be answered. In conclusion, we will cite one sentence by Reynolds and Cook who stated in 1963 that "... oxygen is vitally important in bronchiolitis and there is little convincing evidence that any other therapy is consistently or even occasionally useful".

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