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# Relationship between respiratory syncytial virus bronchiolitis and future obstructive airway diseases

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*Relationship between respiratory syncytial virus bronchiolitis and future obstructive airway diseases. G. Wennergren, S. Kristjánsson. ©ERS Journals Ltd 2001.*
**ABSTRACT: Evidence from a large number of prospective case-control studies shows that respiratory syncytial virus (RSV) bronchiolitis in infancy is often associated with recurrent wheezing and asthma during subsequent years. However, wheezing tends to diminish and most studies show no significant increase in wheezing compared to controls by school age or adolescence. An unresolved question is whether severe RSV infection during infancy causes the respiratory sequelae or inherent abnormalities predispose an infant to develop severe respiratory infection and sequelae, *i.e.* RSV is associated with the development of pulmonary sequelae.**

**Studies on long-term outcome of RSV bronchiolitis are reviewed from an evidence-based perspective.**

**The majority of prospective placebo-controlled studies do not show any long-term beneficial effects of corticosteroid treatment, *i.e.* the risk of subsequent wheezing is not diminished by the treatment. The evidence for an increased risk of allergic sensitization after RSV bronchiolitis is not nearly as strong as the evidence for an increased risk of subsequent wheezing. In fact, most studies do not show any significant increase in atopy after RSV bronchiolitis. This suggests that the increased risk of wheezing after RSV is not linked to an increased risk of atopy. There are some indications that infants who develop severe RSV and subsequent wheezing may have aberrations that predate the RSV infection.**

**To decide whether respiratory syncytial virus bronchiolitis causes, or is associated with the respiratory sequelae (or with subsequent allergy), it will be necessary to conduct prospective, randomized studies, where the cytokine profile prior to bronchiolitis onset is known. Such studies should preferably include some form of intervention against respiratory syncytial virus. A more complete understanding of the risk factors for severe respiratory syncytial virus infection and the role of respiratory syncytial virus infection in the initiation of asthma is needed as a basis for large-scale and cost-effective programmes to prevent respiratory syncytial virus-related morbidity.**
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Respiratory syncytial virus (RSV) bronchiolitis is the most common, severe lower respiratory tract infection in infancy. It now seems well established that RSV bronchiolitis in infancy is associated with recurrent wheezing and asthma during the first decade of life. In some children, wheezing after early lower airway infection with RSV is transient, but in many of the children RSV-induced bronchiolitis represents the onset of asthma. In fact, there are results which indicate that severe RSV bronchiolitis in the young infant may shift the T-helper (Th)1/Th2 balance in favour of a Th2 cytokine pattern, leading to development of allergic sensitization and persistent asthma [1, 2]. However, the association with risk of development of atopy or with asthma in later life is debated [3].

This review gives an overview of the characteristics of the RSV, RSV immunology and RSV bronchiolitis. The main focus, however, is on the relationship between RSV bronchiolitis and subsequent wheezing and asthma, as well as on possible subsequent allergic sensitization. The review also summarizes possibilities for prevention and studies addressing whether corticosteroid treatment of RSV bronchiolitis diminishes the risk of subsequent wheezing.

## The respiratory syncytial virus

### *Respiratory syncytial virus infections*

RSV has been described as the single most important virus causing acute respiratory tract infections

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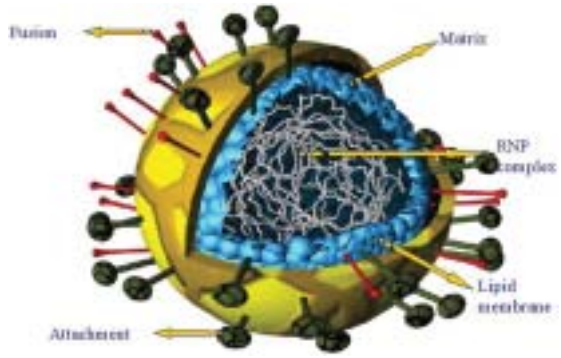


Fig. 1.–Model of the human pneumovirus respiratory syncytial virus (RSV) [7]. The large virion consists of a negative ribonucleic acid genome in a helical nucleocapsid, surrounded by an envelope. Note the attachment (G) glycoprotein and fusion (F) glycoprotein. RNP: ribonucleoprotein.

in infants and toddlers. RSV infections have a seasonal pattern, with annual epidemics during winter and spring in temperate climates, and in the rainy season when the temperature falls in tropical climates. The peak infection rates occur in infants of 6 weeks to 6 months of age. By the age of 2 yrs, ~90% of young children have been infected with RSV [4, 5].

### *The virus*

RSV was first identified in 1956 as the agent that caused chimpanzee coryza [6]. The virus belongs to the Paramyxoviridae family, where it has been assigned a genus of its own, Pneumovirus. RSV is a large virion which consists of a negative RNA genome in a helical nucleocapsid surrounded by an envelope (fig. 1). The envelope contains a viral attachment glycoprotein (G) and a fusion glycoprotein (F). These glycoproteins are the major surface antigenic determinants of RSV. The F and G proteins are vital for the infectivity and pathogenicity of RSV. The F protein is relatively stable, which makes it a suitable target for therapeutic intervention. The G protein is more variable and forms the basis for subgroup classification of RSV into type A and type B. It has been proposed that RSV type A should be the most pathogenic, although current opinion suggests that there are no certain clinical differences between the two subgroups [4, 5].

Paramyxoviridae are transmitted in respiratory droplets and initiate infection in the respiratory tract. The virions penetrate the cell by fusion with the plasma membrane, and the virus replicates in the cytoplasm. Viruses induce cell-to-cell fusion, thereby causing multinucleated giant cells to form. These large fused cells, syncytia, gave RSV its name.

## Respiratory syncytial virus bronchiolitis

The diagnostic term acute bronchiolitis is sometimes used in a rather broad sense to describe virus-induced acute wheezing in infants. However, in the present article the diagnosis "bronchiolitis" is used to denote the acute severe lower respiratory disease, as a rule elicited by RSV, in infants only a few months old.

### *Clinical features of respiratory syncytial virus bronchiolitis*

RSV bronchiolitis typically affects the very young infant, often only 1–3 months old, mostly <6 months of age. RSV infects *via* the upper respiratory tract, particularly through the nasopharynx, and the eyes. The incubation period is 3–5 days. Infection of the bronchiolar epithelial cells results in mucosal inflammation and oedema. Necrosis of epithelial cells and intraluminal plugs, consisting of mucus and cellular debris, cause a ball-valve airway obstruction which leads to hyperinflation of the distal airways and alveoli [4, 5].

The first symptoms of RSV bronchiolitis are coryza and dry cough followed by increasing breathlessness. Sometimes apnoeic spells are observed in the initial stage of the disease in infants <2 months of age, especially in babies born preterm. If fever is present, it is usually low grade. The baby feeds poorly. Hypoxaemia, which often leads to cyanosis, follows, and carbon dioxide retention may lead to hypercarbia. Other clinical symptoms are a sharp, dry cough, tachypnoea and tachycardia. Subcostal and intercostal retractions are seen. The chest becomes hyperinflated due to small airways obstruction and air trapping. Chest radiographs show over-inflated lungs and often perihilar infiltrates. On chest auscultation, fine end-inspiratory crepitations are heard, and the expiratory phase is prolonged. Wheezes may be audible with or without a stethoscope [4].

### *Diagnosis*

RSV is the most common agent, which can be detected in infants with bronchiolitis. The virus can be demonstrated in a positive immunofluorescence antibody or an enzyme-linked immunosorbent assay (ELISA) test performed on nasopharyngeal aspirates or washes, or by cell culture [8]. Overall, RSV has been detected in 40–90% of bronchiolitis cases [9–12]. During the peak of an RSV outbreak, $\geqslant$80% of bronchiolitis cases are associated with RSV [5].

### *Treatment*

The treatment of RSV bronchiolitis is mainly supportive and symptomatic [4]. This includes gentle handling, moderate fluid supply and maintaining oxygenation at arterial oxygen ($O_2$) saturation ($S_{a,O_2}$) $\geqslant$95% by administration of humidified $O_2$. The efficacy of $\beta_2$-agonists in bronchiolitis has been questioned by studies showing no significant effect [13]. A meta-analysis of eight randomized controlled studies, including 324 children <1 yr old, indicates a moderate, short-lasting improvement in symptom score and $S_{a,O_2}$ by inhaled salbutamol (0.1–0.15 mg·kg$^{-1}$

body weight) [14]. Some studies indicate that the effect of inhaled adrenaline or racemic adrenaline is better than that of selective $\beta_2$-agonists, possibly due to the $\alpha$-agonist action of adrenaline. In a double-blind randomized controlled trial (RCT) study, KRISTJÁNSSON *et al.* [15] demonstrated a small, but significant, improvement of oxygenation and symptom score by inhaled racemic adrenaline. In fact, there are four double-blind, RCT studies that report a better effect of inhaled adrenaline or racemic adrenaline, compared to salbutamol, in the treatment of acute bronchiolitis in infants [16–19]. In contrast, almost all placebo-controlled studies on the use of corticosteroids, given by systemic administration or inhalation, show no improvement in the clinical course of acute bronchiolitis [20–24]. VAN WOENSEL *et al.* [25] found that oral prednisolone seemed to accelerate the clinical recovery of children admitted to hospital with RSV bronchiolitis, but the results of that study are an exception. Taken together, the studies indicate that there is no significant effect of corticosteroids in the acute phase of RSV bronchiolitis. The results of antiviral treatment with aerosolized ribavirin are also disappointing. The therapeutic efficacy in the acute infection has been questioned, and in a meta-analysis, no statistically significant effect was demonstrated [26].

## Respiratory syncytial virus-induced inflammation

RSV not only infects the upper airways but also the lower airways, where it causes tissue inflammation and lower airway obstruction. RSV is able to destroy large numbers of epithelial cells. Viral replication in the epithelial cells triggers intracellular signalling pathways, which induce secretion of multiple cytokines, chemokines and adhesion molecules. This is an area where virus and allergen-induced inflammation overlap. Cytokines and chemokines, such as interleukin (IL)-8 and regulated on activation, normal T-cell expressed and secreted (RANTES) increase in airway secretions during viral infections and recruit and activate inflammatory cells such as neutrophils, eosinophils and activated T-cells that have all been linked to asthma [1]. Consequently, elevated levels of eosinophil cationic protein and cysteinyl leukotrienes are found in nasal secretions from infants with RSV infection [27–29]. Elevations are particularly pronounced in bronchiolitis [27, 30].

Release of cysteinyl leukotrienes into the airways during RSV infection may at least partly account for the wheezing observed in bronchiolitis. The mechanism is of particular interest in view of current possibilities for therapeutic intervention with anti-leukotriene drugs [30].

### *Neuroimmune interactions*

Experiments using animal models demonstrate that RSV causes acute and chronic changes in neural control of the airway, altering airway control, resulting in decreased relaxant and increased contractile responses in airway smooth muscle. When infection occurs in early life the alterations persist for long periods [31].

Recent studies indicate that immune and neural mechanisms may be linked and that post-RSV airway inflammation may partly be explained on the basis of such neuroimmune interactions [32]. In lungs from RSV-infected rats, PIEDIMONTE *et al.* [33] have demonstrated an increased vascular permeability elicited by capsaisin stimulation of unmyelinated sensory nerves. The increase in vascular permeability resulted from upregulation of the high-affinity receptor for substance P (the neurokinin (NK)-1 receptor). Such exaggerated neurogenic inflammatory responses can be observed long after RSV has been cleared from the lungs, which suggests that the underlying mechanisms may become independent of the presence of the virus. It is suggested that after resolution of the acute RSV infection, stimulation of the sensory nerves by an airborne irritant may induce inflammation *via* NK-1-expressing T-lymphocytes, which retain a nonspecific memory of the early infectious episode [32].

### *Chronic persistent respiratory syncytial virus infection*

RSV may persist in the infected cells after the initial infection and it may constitute a foreign protein, leading to a chronic inflammation [34, 35]. Guinea pigs, experimentally inoculated with human RSV, show histological evidence of acute bronchiolitis and chronic persistence of viral antigens and viral genome in the lungs [36]. Infected animals develop an anti-RSV immunoglobulin (Ig)-G1 antibody response (the main class of antibody involved in guinea pig allergic responses), histological evidence of acute bronchiolitis, and chronic airway inflammation [36]. RIEDEL *et al.* [37] have demonstrated that in guinea pigs, RSV infection of the airways causes persistent airway hyperresponsiveness (AHR) over a period of $\geqslant 5$ weeks. During this period, viral antigen remained detectable in the lungs and may be responsible for ongoing AHR [37]. From these studies, it appears that persistent RSV lung infection may be important in the pathogenesis of postbronchiolitis wheezing and asthma in children.

### *Surfactant dysfunction*

Regarding nonimmunological factors, VAN SCHAIK *et al.* [38] have suggested that inadequate pulmonary surfactant function may be an important factor in the pathophysiology of RSV-induced bronchiolitis. In experiments with RSV-infected mice, the degree of surfactant dysfunction correlated with the presence of inflammatory cells in bronchoalveolar lavage fluid (BALF) [39]. Surfactant abnormalities have also been demonstrated in infants with severe viral brochiolitis [40].

### Immune responses elicited by respiratory syncytial virus

The possibility that RSV may interact with the immune and respiratory systems in early life to initiate the complex pathogenetic mechanism leading to asthma has been a matter of considerable study and debate. Over 90% of all children are infected with RSV during the first years of life. It has therefore been suggested that if RSV can trigger the "asthmatic process", this will occur in subjects who are predisposed either by their genetic background, or by events occurring before their first encounter with RSV that have "primed" their immune system and lungs [41].

However, it has been demonstrated in animal experiments that RSV has a particular ability to induce production of Th2 cytokines [42], and that RSV infection can increase the risk of allergic sensitization [43, 44]. Since the Th1/Th2 cell balance is regulated by Th1 cytokines suppressing Th2 cells or *vice versa*, a shift in the balance in early life may persist. With this perspective, the effects of early infections will depend on whether they tend to induce Th1 or Th2 cell immunity. Therefore, it has been suggested that early RSV infection interacts with the immune system so that a process leading to allergy, and thereby to asthma, is initiated [2, 45].

In RSV research, particular interest has been devoted to the attachment protein G. In animal models, this protein is able to induce a Th2-like immune response [46, 47]. However, studies to determine whether RSV infections enhance allergy in humans have arrived at different conclusions [2, 3, 45, 48–53]. Since long-term prospective studies have failed to demonstrate a correlation between atopy and RSV-associated wheezing [3, 51, 52], the hypothesis is regarded as controversial [38].

Thus, the key question is whether an abnormal immune response existed before the acute RSV infection or was caused by it. Since almost all children have RSV infections in the first 3 yrs of life, it seems less likely that the infection can be related to the subsequent risk of recurrent wheezing or asthma. Instead, it seems reasonable that the prerequisite for the induction of persistent asthma is a severe infection, which occurs in a child with a genetic predisposition to an atopic phenotype during a vulnerable age interval, the so-called "double-hit hypothesis" [54]. It is also possible that severe RSV lower airway inflammation leads to airway remodelling and affects lung development, or somehow targets allergic inflammation to the lower airways. A third possibility is that children with severe RSV infections have an underlying immune system defect that facilitates allergen sensitization and recurrent wheezing or asthma.

WELLIVER [55] has pointed out that the immune response of the airway to viral infections resembles, in many ways, that after exposure to allergens. WELLIVER [55] concludes that the association between RSV bronchiolitis, in infancy and childhood, is not necessarily one of cause and effect. Instead, it is suggested that the fact that a given host may develop the same type of immune response to viral infections in infancy and to allergen exposures in later childhood offers an alternative explanation for this association. EHLENFIELD *et al.* [56] recently reported that eosinophilia at the time of the RSV bronchiolitis, as a rule, predicts development of airway obstruction later in childhood.

Some evidence for a role of type 2 cytokines in the pathogenesis of bronchiolitis has been provided in human studies. LEGG *et al.* [57] reported a Th2 cytokine profile after early bronchiolitis. RENZI *et al.* [58] have demonstrated that a first episode of bronchiolitis is followed by activation of cellular immunity, and early wheezing in infants is associated with a Th2 response. Lower interferon (IFN)-$\gamma$ production by blood mononuclear cells at the time of bronchiolitis was demonstrated to be an indicator of lower pulmonary function and increased responsiveness to histamine 5 months after bronchiolitis. Furthermore, lower IFN-$\gamma$ production was related to the development of asthma 2 yrs after hospitalization for bronchiolitis [59].

However, VAN SCHAIK *et al.* [38] recently summarized evidence suggesting that the theory that RSV bronchiolitis may result from production of Th2-type cytokines is incorrect, or at least an oversimplification. The authors emphasize that there are studies suggesting that cells producing IFN-$\gamma$ may contribute to RSV-induced wheezing, possibly through induction of leukotriene release, since IFN-$\gamma$ is known to induce mediator release [60]. In a recent study, VAN SCHAIK *et al.* [30] reported increased levels of IFN-$\gamma$ in nasopharyngeal secretions from infants with RSV infection. The highest levels were found in infants with bronchiolitis and recurrent wheezing, while only moderately increased levels were found in children with upper respiratory tract infections. No statistically significant differences in IL-4 concentrations were found between the groups. Experiments in mice found high levels of IFN-$\gamma$ early in the course of experimental infection with RSV [61, 62]. In the experiments by VAN SCHAIK *et al.* [61], IFN-$\gamma$ levels in BALF were significantly correlated to signs of expiratory obstruction. However, in the experiments by SCHWARZE *et al.* [63] IFN-$\gamma$ did not seem to be involved in the development of AHR and airway inflammation in acute RSV infection. Their studies indicate that IL-5 is critical for RSV-induced enhancement of lung eosinophilia and AHR in response to allergic airway sensitization [64]. The presence of IL-4 also seems essential for the development of AHR after RSV infection and subsequent allergic airway sensitization, possibly by enhancing IL-5 production [64]. In contrast, IFN-$\gamma$, the predominant cytokine in acute RSV infection, did not seem to be required for the development of AHR in the mouse model used. On the contrary, the presence of IFN-$\gamma$ appeared to be somewhat protective against these consequences of RSV infection [64].

BJARNARSON *et al.* [28] studied 27 infants <7 months of age, with a RSV infection (mean age 3 months), and found an inverse relationship between IL-4 and IFN-$\gamma$ levels in nasal secretion both from RSV-infected and control infants. However, there was no difference in levels of IL-4 or IFN-$\gamma$ in nasal secretion between the RSV-infected and control groups.

Therefore, increased Th2 and/or decreased Th1 cytokines could not be demonstrated in RSV-infected infants compared with healthy controls, although eosinophil cationic protein levels in nasal secretion were drastically increased in the RSV-infected infants [28].

WELLIVER [65] suggests that it is the infants with atopic predisposition who predominantly develop asthma after RSV infection. Therefore, it is interesting that low levels of the Th1-stimulating cytokine IL-12 have been found in cord blood in children, who later develop RSV bronchiolitis [66]. Low IL-12 production has also been found in infants with severe RSV bronchiolitis [67].

## Postbronchiolitis symptoms

In bronchiolitis we must now contend
with both the disease and the "now" and the "then";
For many such infants a mold has been cast,
perhaps by their unborn and unknown past,
which destines that they shall in time wheeze again.
For them this disease
is the distant, boding knell
Of vulnerable lungs
to a microbe's mystic spell. C.B.H. [68].

### *Postbronchiolitis effects on hyperresponsiveness and lung function*

It is well known that viral respiratory infections transiently increase bronchial reactivity [69]. This was observed in normal subjects after upper respiratory infections >35 yrs ago [70].

Several long-term follow-up studies of bronchial reactivity, after hospitalization with proven RSV bronchiolitis, have reported bronchial hyperresponsiveness to exercise and histamine several years later, even at school age [48, 49, 53, 71]. However, in mild cases there seemed to be no hyperresponsiveness present at 8–12 yrs follow-up [72, 73].

Most follow-up studies of RSV bronchiolitis in infancy show that forced expiratory flow rates (*e.g.* forced expiratory volume in one second (FEV1), are lower at school age compared with control groups [74]. KATTAN *et al.* [72] demonstrated early on that children who had been hospitalized for RSV bronchiolitis as infants, later had lung function abnormalities similar to those found in children with asthma. Decreased expiratory flow rates in children with a history of bronchiolitis, compared with controls, have also been reported in other follow-up studies [48, 49].

### *Respiratory syncytial virus bronchiolitis and subsequent wheezing*

As long as 40 yrs ago, WITTIG and GLASER [75] and EISEN and BACAL [76] reported that bronchiolitis in infancy was often followed by recurrent episodes of wheezing. In 1971, ROONEY and WILLIAMS [77] reported that 56% of children who had been hospitalized with RSV bronchiolitis as infants had multiple wheezing episodes 2–7 yrs later. A family history of asthma was present in 72% of the patients who had recurrent wheezing episodes, compared with 18% of patients where no subsequent wheezing had occurred. After that study some 30 yrs ago, several controlled follow-up studies were performed. In a 10-yr follow-up, PULLAN and HEY [49] reported that 42% of children with a history of RSV bronchiolitis in infancy had had further episodes of wheezing, while only 19% of controls had ever wheezed. The difference between RSV and control groups was most pronounced during the first 4 yrs of life, and many children with recurrent wheezing during that time had stopped wheezing by the time they were 6 yrs old. At 10 yrs, asthma was diagnosed in 6.2% of the bronchiolitis group *versus* 4.5% in the control group. Similar results were presented by MOK and SIMPSON [50] in a 7-yr follow-up; however, the outcome of RSV-induced bronchiolitis, pneumonia or bronchitis in infancy was not separated in that study. MCCONNOCHIE and ROGHMANN [78] studied cases of mild bronchiolitis in infancy not requiring hospitalization, and they found a significantly increased risk of wheezing at 8 yrs of age. However, the relative risk of wheezing decreased during the following years, and by the time the children were 13 yrs old the relative risk of asthma was no longer significantly increased compared with the controls [78]. A study that has been particularly valuable to shed light on the natural history of childhood wheezing is the longitudinal Tucson study [3]. In that study, STEIN *et al.* [3] reported that early lower airway infection with RSV is an independent risk factor for recurrent wheezing up to the age of 11 yrs, but not at 13 yrs. Thus, children with a history of bronchiolitis tend to have recurrent episodes of wheezing or asthma although episodes of wheezing tend to diminish by adolescence [79]. Nonetheless, it is important to realize that otherwise healthy children treated for an early RSV infection constitute only a minority, at most 10%, of the children who will be treated for obstructive airways disease later on.

In the Swedish study by SIGURS *et al.* [2], asthma was significantly more common by the age of 7 yrs among the group of children who had been hospitalized with severe RSV bronchiolitis as young infants, 23% having current asthma *versus* 2% in the control group (fig. 2). Corresponding figures for cumulative asthma were 30% *versus* 3%.

SIGURS *et al.* [2] also report that the development of asthma is often seen in the group of children who have had bronchiolitis, but who lack heredity for asthma. The conclusion of the Swedish investigators is that the early RSV bronchiolitis has induced a process which has led to asthma.

KNEYBER *et al.* [80] recently published a meta-analysis from six follow-up studies of RSV bronchiolitis published between 1978–1998 [45, 48–50, 53, 81] (fig. 3). For all of these studies, postnatal age of initial illness was <12 months, all children were hospitalized for RSV bronchiolitis in infancy, the diagnosis RSV was virologically confirmed, and a control group

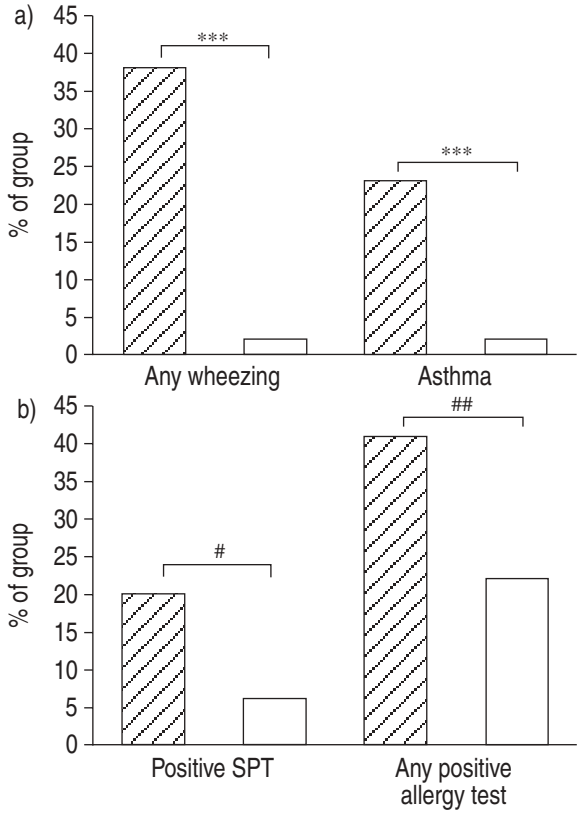


Fig. 2.–The course of a) bronchial obstructive disease and b) allergic sensitization up to the age of 7.5 yrs in children with respiratory syncytial virus (RSV: ▨) bronchiolitis in infancy and a control group (□) [2]. a) Rates of current wheezing and of current asthma in the 47 RSV children and the 93 control children at the age of 7.5 yrs. b) Rates of a positive skin-prick test (SPT) to common inhaled allergens and of "any positive allergy test" in 44 RSV children and 89 (SPT) and 86 (any positive test) control children at the age of 7.5 yrs. ***: p<0.001; #: p=0.014; ##: p=0.039.

was used. The meta-analysis confirms that wheezing is common after RSV bronchiolitis in infancy and may persist for ⩾5 yrs of follow-up. Up to 5 yrs of follow-up after the RSV bronchiolitis, 40% of children reported wheezing, compared with only 11% in the control group (p<0.001). Between 5–10 yrs of follow-up, 22% of the bronchiolitis group reported wheezing, compared with 10% of the control group (p=0.19). The incidence of recurrent wheezing as defined by ⩾3 wheezing episodes, also decreased with increasing years of follow-up, and ⩾5 yrs 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. KNEYBER *et al.* [80], therefore, concluded that it was unlikely that RSV bronchiolitis is a cause of atopic asthma later in life. Table 1 summarizes the studies on RSV bronchiolitis and the occurrence of subsequent wheezing.

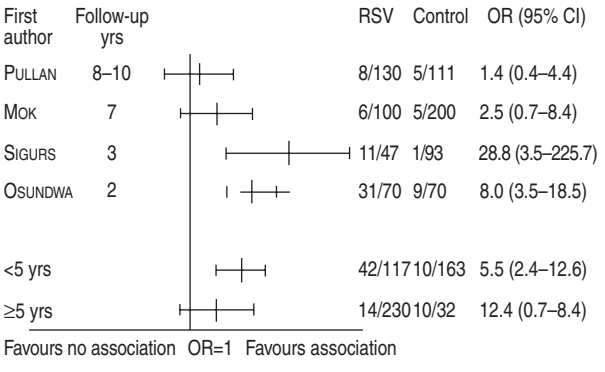


Fig. 3.–Relationship between respiratory syncytial virus (RSV) bronchiolitis in infancy and recurrent wheezing during childhood. Odds ratios (ORs) with 95% confidence intervals (CIs) are indicated. The vertical continuous line represents OR=1. No significant difference between the RSV bronchiolitis and the control group was seen by 5 yrs of follow-up [80].

To conclude, several prospective case-control studies of high quality show that RSV bronchiolitis is often associated both with recurrent wheezing and asthma during a period of several years after the illness. However, wheezing tends to diminish, and most studies show no significant increase in wheezing by school age or adolescence compared with controls.

### *Does wheezing occur exclusively subsequent to respiratory syncytial virus bronchiolitis?*

The association between virus infections and wheezing is also obvious later on during early childhood [8, 82, 83]. ERIKSSON *et al.* [84] pointed out that, regardless of whether a group was recruited according to confirmed aetiology, such as RSV [45, 85, 86], or according to clinical symptoms (lower respiratory tract infection) [53, 83, 87], follow-up studies showed that at least 50% of the children studied had recurrent wheezing episodes. The authors, therefore, addressed the question of whether lower respiratory tract infection with RSV was more likely to induce later wheezing than other viruses [84]. Hence, they examined the risk of subsequent wheezing in young children hospitalized for influenza A or RSV infection during a season with outbreaks of RSV and influenza A. Children with RSV were younger than those with influenza A (mean age 2.2 *versus* 11 months); otherwise, there was no major difference between the RSV and influenza A groups with respect to patient characteristics or environmental risk factors. The authors found no influence on the risk of later wheezing from type of viral infection. Sixty per cent of children had two or more episodes of wheezing after either influenza A or RSV. Obviously, the ages of the studied groups differed and the study does not say anything about similarities or differences in the mechanisms behind the subsequent wheezing. However, the study does illustrate that a tendency to subsequent wheezing is not a phenomenon exclusive for severe RSV infection.

A Swedish longitudinal study included all children admitted to hospital due to wheezing bronchitis before the age of 2 yrs (30% with RSV) [83]. Thirty per cent of the children had persistent asthma at the age of 10 yrs [88]. Children, in whom RSV was

Table 1. – Studies on respiratory syncytial virus (RSV) bronchiolitis and occurrence of subsequent wheezing

| First author [ref. no.] | Design | Patients/ controls n | RSV-positive patients % | Age at bronchiolitis | Follow-up time yrs | End-point | Results at time of follow-up |
|---|---|---|---|---|---|---|---|
| PULLAN [49] | Case-control follow-up study | 130/111 | 100 | 3.5 months | 10 | Asthma | 6.2% *versus* 4.5% had asthma at the age of 10 |
| MOK [50] | Case-control follow-up study | 100/200 | 100 | 4.3 months[#] | 7 | Asthma | 6.0 *versus* 2.5% had asthma at the age of 7 |
| CARLSEN [51] | Prospective case-control study | 51/24 | 61 | 6 months | 2 | Episodes of BPO | >3 episodes of BPO in 60% of index children *versus* one episode among controls** |
| MCCONNOCHIE [78] | Historical cohort study | 51/102 | No viral isolates | <24 months | | Asthma and any wheezing | Significant difference in wheezing and asthma at age 8 but not at age 13 |
| | | | | | 8 | | Asthma 19.6% *versus* 6.9%**, RR 2.8 |
| | | | | | | | Any wheezing 41.2% *versus* 17.6%[¶], RR 2.3 |
| | | | | | 13 | | Asthma 15.7 % *versus* 8.8 %[+], RR 1.8 |
| | | | | | | | Any wheezing 31.4% *versus* 21.6%[+], RR 1.45 |
| OSUNDWA [81] | Retrospective case-control study | 70/70 | 100 | 3.8 months (3–8) | 2 | Recurrent wheezing | 44% of infants with RSV bronchiolitis developed recurrent wheezing *versus* 12.9% of controls[f] |
| SIGURS [45] | Prospective case-control study | 47/93 | 100 | All <12 months mean 3.5 months | 3 | Asthma | Asthma in 23% of RSV group *versus* 1% of controls*** RR 21.8 (2.9–163) |
| | | | | | | Any wheezing | Any wheezing, 60% *versus* 32%[§], RR 1.9 (1.3–2.7) |
| SIGURS [2] | Prospective case-control study | 47/93 | 100 | All <12 months mean 3.5 months | 7.5 | Asthma | Current asthma in 23% of RSV group *versus* 2% of controls**, RR 10.9 (2.5–47.1) |
| | | | | | | Any wheezing | Any wheezing (current), 38% *versus* 2%[¶], RR 17.8 (4.3–73.5) |
| STEIN [3] | Longitudinal cohort study | | 100 | Lower respiratory tract illness before age 3 yrs | | Frequent wheezing | RSV lower RTI associated with four-fold increased risk of frequent wheezing by age 6. Risk decreased markedly with age and was not significant by age 13. |
| | | 68/669 | | 6 yrs | | | OR 4.3 (2.2–8.7) |
| | | 56/545 | | 8 yrs | | | OR 1.9 (0.9–4.2) |
| | | 79/634 | | 11 yrs | | | OR 2.4 (1.3–4.6) |
| | | 49/469 | | 13 yrs | | | OR 1.4 (0.7–2.6) |
| KNEVBER [80] | Meta-analysis of four controlled studies [45, 49, 50, 78] | | | | | Recurrent wheezing | |
| | | 117/163 | 100 | <12 months | <5 | Recurrent wheezing | Up to 5 yrs recurrent wheezing significantly more common in the RSV group, 40% *versus* 11%, OR 5.5 (2.4–12.6) |
| | | 230/321 | 100 | <12 months | ⩾5 | Recurrent wheezing | By 5 yrs of follow-up, no significant difference between RSV and control groups regarding recurrent wheezing, OR 2.4 (0.7–8.4) |

BPO: bronchopulmonary obstruction; RR: relative risk; OR: odds ratio; RTI: respiratory tract infection. [#]: acute lower RTI; [+]: nonsignificant. **: $p<0.01$; ***: $p<0.001$; [¶]: $p<0.0001$; [§]: $p=0.003$; [f]: $p=0.001$.

detected at admission to the study, were not over represented as compared with children in whom other viral agents were detected at first admission. Instead, persistent asthma correlated significantly with the recent presence of other atopic diseases in the subjects. Similar results have been presented by KORPPI and co-workers [87, 89]. The findings of these studies fit better with the view that asthma developed in predisposed children rather than with the hypothesis that RSV infection induced a process leading to persistent asthma. In conclusion, lower respiratory tract infections in young children, including those elicited by viral agents other than RSV, are often followed by repeated wheezing episodes.

### *Respiratory syncytial virus bronchiolitis and subsequent allergic sensitization*

Development of asthma and development of allergies are not identical. As mentioned previously, it has not been clearly established whether the increased risk of subsequent wheezing after RSV bronchiolitis is linked to an increased risk of allergic sensitization. Most studies do not report an increased risk of allergic sensitization in children with a history of RSV bronchiolitis (table 2). An increased risk of allergic sensitization was not found in the Tucson study [3]. In the study group followed by SIGURS *et al.* [2], an increased allergic sensitization seemed to be evident both from positive skin-prick tests and from "any positive allergy test" (fig. 2). By the age of 7 yrs, current atopic asthma was found in 8.5% of cases *versus* 1% in the control group. Allergic rhinoconjunctivitis was found in 14.9% of cases *versus* 2% of the controls, while the prevalence of atopic dermatitis was similar in the two groups. In addition to SIGURS *et al.* [2], MURRAY *et al.* [53] reported an increased risk of skin-prick test sensitization at the age of 6 yrs. However, when the same children were re-investigated at 10 yrs of age, an increased risk was no longer found [52] (table 2).

As can be concluded from the summary of studies presented in table 2, the evidence for an increased risk of allergic sensitization is not nearly as strong as the evidence for an increased risk of subsequent wheezing. In fact, most studies do not show a significant increase in personal atopy. Thus, it can be concluded that the increased risk of subsequent wheezing after RSV is not linked to an increased risk of atopy.

### *Possible reason for the difference in outcomes*

A possible reason for diverging outcomes in different follow-up studies of early RSV infection is varying severity of the initial infection. Some 80–90% of children are infected with RSV during infancy [4, 5]. Most have a subclinical or mild upper airway infection. Only a fraction of the children have lower respiratory airway infection; the prevalence has been estimated at 10–40%. Some 5% develop more severe lower airway symptoms. About 1–2% are hospitalized, and only a minority of the hospitalized children require intensive care. Such differences are likely to influence the outcome of the infection. Thus, the results from studies of children hospitalized for severe RSV bronchiolitis will probably differ from children seen as outpatients for wheezing, and most certainly from those only reported by parents as having had wheezing in the first year of life [90]. It is likely that it is in severe early RSV infections that the virus is able to alter the response of the host to the current infection as well as to subsequent infections [2, 45]. The difference in results between, for example, the Tuscon study by STEIN *et al.* [3] and the Swedish studies by SIGURS and co-workers [2, 45], may have occurred because the Tuscon study seems to be based on relatively mild cases of bronchiolitis, while the Swedish studies concerned severely ill infants needing hospitalization.

### *Causation or association?*

As pointed out by LONG *et al.* [85] and SIGURS *et al.* [2], descriptive studies can suggest connections between RSV and subsequent symptoms. MCBRIDE [90] states that since most studies have been observational, the fundamental question of causation *versus* association remains unresolved. Does severe RSV infection during infancy cause the differences in pulmonary function observed later in life, or do inherent abnormalities predispose an infant to develop severe lower respiratory tract infection, in which case RSV is associated with the development of pulmonary sequelae (fig. 4)? However, the majority of studies indicate that the infant, who develops severe RSV and subsequent wheezing, does have differences which predate the RSV infection. This supports the "association" hypothesis.

The strongest study design to prove causation would be a controlled clinical trial, in which subjects are randomly assigned to an intervention. If results for the intervention group and those for the control group differ, causation is demonstrated. A conclusive intervention study would need to be a major investigation, and the subjects would have to be monitored for many years. Such interventions include methods of preventing RSV disease by passive or active immunization. Until such large intervention trials can be carried out, it remains uncertain whether impaired lung function in children with a history of RSV bronchiolitis represents differences that predate the early RSV infection, or are caused by it [90].

## Prevention

The F and G surface glycoproteins of the RSV induce protective neutralizing antibodies. However, the protective immunological response is incomplete. Therefore, infections with RSV occur annually during the first years of life, often with the same strains of virus. Strategies to prevent severe respiratory illnesses in infancy, by prophylactic administration of immunoglobulin, vaccination or antiviral medication, could potentially reduce the incidence of asthma in childhood.

Table 2. – Risk of allergic sensitization after respiratory syncytial virus (RSV) bronchiolitis in infancy as reported by different studies

| First author [ref. no.] | Design | Patients/ controls n | RSV-positive patients % | Age at bronchiolitis | Follow-up time yrs | End-point | Result at time of follow-up |
|---|---|---|---|---|---|---|---|
| Studies not demonstrating any increased risk at time of follow-up | | | | | | | |
| SIMS [48] | Case-control follow-up study | 35/35 | 100 | <12 months | 8 | Personal history of atopy | The prevalence of clinical features of atopy was similar in bronchiolitis and control groups |
| PULLAN [49] | Case-control follow-up study (extension of [48]) | 130/111 | 100 | 3.5 months | 10 | Eczema or rhinitis | No significant difference between RSV and control groups, 19% *versus* 15% |
| MOK [50] | Case-control follow-up study | 100/200 | 100 | 4.3 months[#] | 7 | Atopy | Atopic characteristics were similar between RSV and control groups, but figures not given |
| CARLSEN [51] | Prospective case-control study | 51/24 | 61 | Median 6 months | 2 | Total IgE, eosinophil counts | No significant difference between index and control group in atopic eczema or urticaria, positive SPT, total IgE or eosinophil counts |
| NOBLE [52] | Prospective case-control study | 61/47 | 66 | All <12 months, mean 4 months | 9–10 | Positive SPT | No difference between bronchiolitis and control group, 31% *versus* 30% positive SPT |
| STEIN [3] | Longitudinal cohort study | | 100 | Lower RTI before age 3 yrs | | Positive allergy SPT | No association between RSV lower RTI and subsequent atopic status by age 6 or 11 yrs |
| | | 155/272 | | | 6 | | 37.4% (RSV) *versus* 39.7% (controls) |
| | | 145/253 | | | 11 | | 59.3% (RSV) *versus* 58.9% (controls) |
| KNEYBER [80] | Meta-analysis of three controlled studies [45, 48, 49] | 212/239 | 100 | All <12 months | | Personal history of atopy | No significant difference between RSV and control groups 15% *versus* 17%, OR 0.7 (0.4–1.1) |
| Studies demonstrating an increased risk at time of follow-up | | | | | | | |
| MURRAY [53] | Prospective case-control study | 73/73 | 68 | All <12 months, mean 4 months | 6 | Personal atopy (eczema and/or SPT) | Personal atopy more prevalent in the bronchiolitis group, 37% positive *versus* 20.5% (controls)* |
| SIGURS [45] | Prospective case-control study | 47/93 | 100 | All <12 months, mean 3.5 months | 3 | | Allergic sensitization more common in the RSV group |
| | | 45/92 | | | | Positive SPT (inhalants) | 13% (RSV) *versus* 1% (controls)[¶], RR 12.3 (1.5–98.9) |
| | | 44/92 | | | | Any positive allergy test | 32% (RSV) *versus* 9% (controls)[+], RR 3.7 (1.7–8.1) |
| SIGURS [2] | Prospective case-control study | | 100 | All <12 months, mean 3.5 months | 7.5 | | Allergic sensitization more common in the RSV group |
| | | 44/89 | | | | Positive SPT | 20% (RSV) *versus* 6% (controls)[§], RR 3.6 (1.3–10.2) |
| | | 44/86 | | | | Any positive allergy test | 41% (RSV) *versus* 22% (controls)[ƒ], RR 1.9 (1.1–3.2) |

RTI: respiratory tract infection; SPT: skin-prick test; IgE: immunoglobulin-E; OR: odds ratio; RR: relative risk. [#]: acute RTI. *: $p<0.05$; [¶]: $p=0.005$; [+]: $p=0.002$; [§]: $p=0.014$; [ƒ]: $p=0.039$.

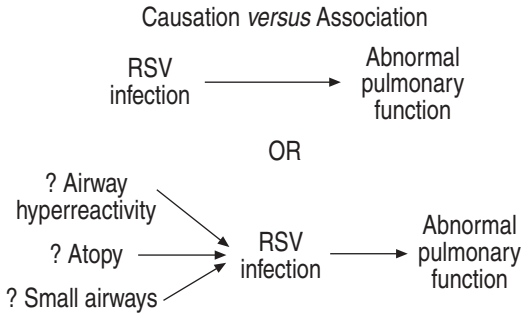


Fig. 4. – A link between severe respiratory syncytial virus (RSV) bronchiolitis in infancy and development of reduced pulmonary function and wheezing later in childhood is established. However, it is unclear whether RSV infection causes the sequelae or whether underlying abnormalities, when coupled with severe RSV bronchiolitis early in life, contribute to respiratory sequelae in later childhood [90].

*Monoclonal antibodies*

Administration of a humanized monoclonal neutralizing antibody to RSV, palivizumab, has proved to be an effective strategy to prevent RSV infection in premature and high-risk infants. Palivizumab has a strong binding affinity to the F protein and prevents the RSV spreading into the lower airways. The infant must receive the injections at regular monthly intervals throughout the RSV season to maintain optimal RSV protection. In the IMpact study [91], the incidence of RSV-related hospital admission was reduced by 55% in the studied risk groups (prematurity, <36 gestational weeks, or bronchopulmonary dysplasia). In absolute figures, the rate of hospital admission in the placebo group was 10.6% *versus* 4.8% in the palivizumab-treated group. The treatment is expensive, which limits large-scale use.

*Antiviral treatment*

Aerosolized ribavirin, a synthetic purine nucleotide derivative of guanosine, is the only antiviral drug available for treatment of severe RSV infections in infants and young children. It is virustatic, and its therapeutic efficacy in the acute infection is limited. Follow-up studies of the effect of ribavirin treatment on respiratory sequelae of RSV bronchiolitis show conflicting results. In a randomized placebo-controlled trial, LONG *et al.* [92] were unable to demonstrate any statistically significant difference in pulmonary function 10 yrs after RSV bronchiolitis was treated with ribavirin or placebo. Similarly, KRILOV *et al.* [93] found no statistically significant difference in reactive airway disease between treatment groups, 5–6 yrs after RSV bronchiolitis. In contrast, a prospective 5–7-yr follow-up study by RODRIGUEZ *et al.* [94] of a placebo-controlled randomized trial suggested that ribavirin provides a long-term benefit *versus* placebo. A follow-up by EDELL *et al.* [95] also suggested that ribavirin treatment of RSV bronchiolitis could reduce the prevalence of subsequent reactive airway disease.

*Vaccines*

The development of a vaccine for RSV remains an important goal in view of the clinical importance of the pathogen. A protective live attenuated vaccine that is administered at, or shortly after, birth would be ideal. Maternal immunization in the third trimester is also a possible alternative [96]. Since young children have repeated RSV infections, the vaccine must produce better protection than is induced by natural RSV infection. Otherwise recurrent infections will not be hindered. Inhibiting antibodies from the mother are an obstacle to immunization of the baby, if the vaccine is given shortly after birth. Vaccines for RSV are under development [97]. However, attempts to develop attenuated vaccines have, so far, not resulted in a commercially-available vaccine.

Although the development of effective virus vaccines is one of the major successes of biomedical research, an early vaccine for RSV has provided an example of unexpected, serious safety problems. Some children, who were immunized with an inactivated vaccine against RSV, developed a more serious infection than the nonvaccinated children when they came into contact with the wild-type virus. It is possible that the chemical inactivation had led to distortion of the immune response so that excessive production of IgE against one of the surface proteins occurred.

The use of recombinant DNA technology to produce RSV vaccine is now being studied. Such attempts concentrate on alterations of the extracellular domain of the F protein. Antibodies to the F protein are generally cross-reactive to both of the major RSV strains, A and B. Therefore, the F protein has been especially in focus in the development of recent candidate vaccines [98–101].

*Can corticosteroid treatment of respiratory syncytial virus bronchiolitis diminish the risk of subsequent wheezing?*

Several placebo-controlled studies have addressed the question whether corticosteroid treatment can influence the degree of respiratory sequelae after RSV bronchiolitis. Table 3 summarizes these studies. The results are not consistent, although most follow-up studies report negative results [20, 21, 24, 102, 103]. In a British study, early treatment with nebulized budesonide for 6 weeks neither decreased acute bronchiolitis symptoms (83% RSV positive) nor prevented postbronchiolitic wheezing during the following 6 months [20]. In a Danish study, oral prednisolone treatment of children <24 months of age, hospitalized because of acute RSV infection, had no effect on outcome measures, either in the acute phase or in follow-ups, 1 month and 1 yr after admission to hospital [21]. Similarly, a recent Dutch study found that oral prednisolone administered during the acute phase of RSV bronchiolitis did not prevent postbronchiolitis wheezing or asthma at the mean age of 5 yrs [102]. In a British study, FOX *et al.* [103] studied the effect of administering inhaled

Table 3. – Effect of corticosteroid treatment of respiratory syncytial virus (RSV) bronchiolitis on the risk of subsequent wheezing; outcome in placebo-controlled studies

| First author [ref. no.] | Design | Patients active treatment/placebo n | RSV-positive % | Age at enrolment, mean/median months | Treatment | Follow-up time | Result at time of follow-up |
|---|---|---|---|---|---|---|---|
| Studies not demonstrating any effect at time of follow-up | | | | | | | |
| BÜLOW [21] | RCT | 73/74 | 100 | 5.5 | Oral prednisolone for 5 days | 1 yr | No effect of the treatment |
| VAN WOENSEL [102] | RCT | 24/23 | 100 | 3.6 | Oral prednisolone acutely for 7 days | 5 yrs | No significant difference in transient, persistent or late-onest wheezing, 8% *versus* 17%, 42% *versus* 31% and 17% *versus* 13%[#] |
| CADE [24] | RCT | 82/79 | 100 | 4 | Nebulized budesonide until 2 weeks after discharge | 1 yr | No long-term benefits of the active teatment |
| RICHTER [20] | RCT | 21/19 | 83 | 3.5 | Nebulized budesonide for 6 weeks | 6 months | No prevention of postbronchiolitic wheezing |
| FOX [103] | RCT | 25/24 | 65 | 2.5 | Inhaled budesonide for 8 weeks | 1 yr | Treated infants did not have less postbronchiolitic wheezing |
| REIJONEN [104] | RCT | 31/28 | 26 | 10.6 | Nebulized budesonide for 4 months | 1 yr | The treatment did not significantly decrease occurrence of asthma 1 yr later |
| REIJONEN [105] | RCT | 31/29 | 26 | 10.6 | Nebulized budesonide for 4 months | 3 yr | Nebulized corticosteroids for 4 months had no influence on the occurrence of asthma 3 yrs later |
| Studies demonstrating positive effect at time of follow-up | | | | | | | |
| KAJOSAARI [106] | RCT | 71/38 | 100 | 2.6 | Nebulized budesonide for 7 days or 2 months | 2 yrs | Fewer treated children on continuous asthma medication |
| CARLSEN [107] | RCT | 22/22 | No percentage given | 15.7 | Nebulized BDP for 8 weeks | 14 weeks | Fewer obstructive symptoms during the follow-up period |
| REIJONEN [89] | RCT | 31/30 | 26 | 10.6 | Nebulized budesonide for 4 months | Weeks 9–16 | Treated children had fewer wheezing episodes and hospital admissions. Particularly children with atopy benefited. |

RCT: randomized controlled trial; BDP: beclomethasone diproprionate. [#]: active *versus* placebo.

budesonide for 8 weeks after hospital admission with acute viral bronchiolitis. Incidence of coughing or wheezing was not reduced for ⩽12 months after bronchiolitis. CADE *et al.* [24] in another British study, also failed to find any short- or long-term clinical benefit of administration of nebulized corticosteroids in the acute phase of RSV bronchiolitis.

A few studies report positive long-term effects on postbronchiolitic wheezing after corticosteroid treatment. KAJOSAARI *et al.* [103] recently reported results indicating that inhaled corticosteroid treatment during and after the acute phase of RSV bronchiolitis in infancy (mean age 2.6 months) may have a beneficial effect on subsequent bronchial wheezing. The 117 children were followed up to 2 yrs after the bronchiolitis episode. In the group of children who had received inhaled budesonide for a week during the acute episode, 18% developed asthma; the figure for those treated with nebulized budesonide for 2 months was 12%. The corresponding figure for asthma development in the group that only received symptomatic treatment was significantly higher at 37%. The authors report that the children who seemed to benefit most from the treatment were those with atopy. In addition, a recent Swedish non-RCT follow-up study 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 (median age at hospitalization 2–3 months) [108]. In conclusion, however, the majority of prospective placebo-controlled studies do not show any long-term beneficial effects of steroid treatment for RSV bronchiolitis.

The effect of anti-inflammatory treatment for older infants admitted to hospital with wheezing has also been investigated. Finnish studies have found that 4 months of treatment with nebulized budesonide reduced the recurrence of wheezing initially [89]. However, the beneficial effect disappeared shortly after termination of the treatment (the children had a mean age of 10.6 months at inclusion and RSV had been detected in 26%) [104]. In addition, the anti-inflammatory therapy had no influence on the occurrence of asthma 3 yrs later [105].

## Conclusions

A child with a history of RSV bronchiolitis is more likely to have repeated wheezing and asthma than the average child. Evidence from a large number of prospective case-control studies of high quality show that RSV bronchiolitis is often associated with recurrent wheezing and asthma during several subsequent years. However, wheezing tends to diminish and most studies show no significant increase in wheezing by school age or adolescence compared with controls. It remains unresolved whether severe RSV infection during infancy causes the differences in pulmonary function observed later in life or whether inherent abnormalities predispose an infant to develop severe lower respiratory tract infection, in which case RSV is associated with the development of pulmonary sequelae. Some studies indicate that many infants who develop severe RSV and subsequent wheezing do have differences which predate the RSV infection.

Opinions differ concerning whether RSV bronchiolitis is linked to an increased risk of allergic sensitization or not. The evidence for an increased risk of allergic sensitization is not nearly as strong as the evidence for an increased risk of subsequent wheezing. In fact, most studies do not show a significant increase in atopy after RSV bronchiolitis. This indicates that the increased risk of subsequent wheezing after RSV is not linked to an increased risk of atopy.

Several prospective placebo-controlled studies have addressed whether corticosteroid treatment influences the degree of respiratory sequelae after RSV bronchiolitis. The majority of these studies do not show any long-term beneficial effect of steroid treatment.

To decide whether respiratory syncytial virus bronchiolitis causes, or is associated with, the respiratory sequelae or with subsequent allergy, it will be necessary to conduct prospective, randomized studies, where the cytokine profile prior to bronchiolitis is known, and which include some forms of intervention against respiratory syncytial virus, such as prophylactic administration of neutralizing antibodies or vaccination against the virus. A more complete understanding of the risk factors for severe respiratory syncytial virus infection and the role of respiratory syncytial virus infection in the initiation of asthma is needed as a basis for large-scale and cost-effective programmes to prevent respiratory syncytial virus-related morbidity.

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