Lower respiratory tract infection caused by respiratory syncytial virus. The short-term and the long-term efficacy of corticosteroids
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Chapter 6
The long-term effect of prednisolone in the acute phase of bronchiolitis caused by respiratory syncytial virus

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Abstract

Background
Follow-up studies have demonstrated that bronchiolitis caused by respiratory syncytial virus (RSV) is strongly associated with wheezing in the ensuing years. During the acute infection the immune response may induce long-lasting detrimental effects, thereby contributing to post-bronchiolitic wheezing (PBW). Therefore, immune modulating drugs like corticosteroids administered in the acute phase of RSV bronchiolitis may prevent PBW and asthma. To evaluate this we performed a controlled prospective follow-up study up after a randomised double-blind placebo-controlled intervention in the acute phase with oral prednisolone.

Methods
Fifty-four patients under 2 years of age, hospitalised for RSV bronchiolitis between 1992 and 1995 were randomised to prednisolone (1 mg/kg/day, orally during 7 days) or placebo. At the mean age of 5 years, 47 patients completed follow-up. Patients were divided into 4 groups: no wheezing, transient wheezing (wheezing during the first year of life), persistent wheezing (wheezing during the first year of life and asthma at the age of 5) and late-onset wheezing (no wheezing during the first year of life but asthma at the age of 5). Prevalence of wheezing and asthma were investigated through an interview by telephone using a standardised questionnaire.

Results
We found no statistically significant differences between the prednisolone and the placebo group in the number of patients with transient wheezing (8% vs. 17%), persistent wheezing (42% vs. 31%), or late-onset wheezing (17% vs. 13%).

Conclusions
We conclude that oral prednisolone during the acute phase of RSV bronchiolitis is not effective in preventing PBW or asthma at the mean age of 5 years.

Introduction
Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infection in infants and young children. Follow-up studies have demonstrated that RSV bronchiolitis is strongly associated with increased airway responsiveness and wheezing during the ensuing years (post-bronchiolitic wheezing), and even with the development of asthma later in childhood.

The debate in the literature continues as to whether RSV bronchiolitis early in life is the first manifestation of asthma or whether RSV bronchiolitis causes post-bronchiolitic wheezing (PBW) and subsequently asthma. Results of several studies support the first theory that some children have a genetic predisposition for wheezing.
during and after RSV infections. In addition, it has been demonstrated that a reduced lung function already exists before the first RSV infection in infancy. Other studies are more supportive for the theory that direct viral injury of the airway epithelium as well as the immune response may contribute to wheezing, airflow limitation, and increased airway responsiveness during and after RSV infection. An increasing amount of evidence has demonstrated that the immune response may play a detrimental role during RSV bronchiolitis. Although the immune response leads to clearance of the virus, it also contributes to the pathogenesis of RSV lower respiratory tract infection. Several inflammatory cells and mediators released during acute infection play a role in this immune injury that leads to airway inflammation and airway responsiveness. The effects of this immune injury may not only play a role during the acute phase of RSV bronchiolitis, but may also be long-lasting, thus contributing to PBW and asthma. Because RSV bronchiolitis is, in part, an immune mediated disease, immune modulating drugs like corticosteroids may be effective during the acute phase of RSV bronchiolitis (short-term effect), and it is speculated that they may also prevent PBW and asthma (long-term effect). The effect of inhaled corticosteroids on the incidence of PBW has been evaluated in several trials with conflicting results. The effect of systemic corticosteroids during the acute phase of bronchiolitis on PBW and the development of asthma has not been studied before. To evaluate this we performed a follow-up study after double-blind placebo-controlled intervention with oral prednisolone in children hospitalised for proven RSV bronchiolitis. The short-term effects have been described earlier. Briefly, we found that corticosteroids may be an effective treatment in patients with severe bronchiolitis leading to a faster clinical recovery in non-ventilated patients and a shorter duration of hospitalisation in ventilated patients. In this follow-up study we investigated the effect of prednisolone vs. placebo during the acute phase of RSV bronchiolitis on the prevalence of wheezing during the first year of life and asthma at the age of 5 years.

Methods

Study design
All patients younger than 2 years with microbiologically proven RSV bronchiolitis admitted to the Beatrix Children's Hospital (Groningen, the Netherlands) between December 1992 and April 1995 were included after written informed consent was obtained from the parents or caretakers. Bronchiolitis was defined as the first attack of acute tachypnea, wheezing and/or decreased breathing sounds, cyanosis and the use of accessory respiratory muscles in the presence of an apparent viral infection. RSV infection was confirmed by direct immunofluorescence assay using fluorescein isothiocyanate labeled monoclonal antibodies of Imagine (Novo Nordisk Diagnostics Ltd, Cambridge, United Kingdom). Patients who had used corticosteroids
(systemic or by inhalation) during the 2 months before admission were excluded. Patients were randomly allocated to the treatment group or the placebo group by the hospital pharmacy. The study treatment was oral prednisolone powder (1 mg/kg/day in two divided doses for 7 days) or placebo. Treatment was started within 24 hours after admission.

Efficacy analysis
For the data collection of this follow-up study parents or caretakers of the former bronchiolitis patients were interviewed by telephone. Interviews took place from August 1998 until April 1999. An extended Dutch version of the standardised questionnaire of the British Medical Research council and the Dutch version of the European Community Respiratory Health Survey questionnaire was used. The questionnaire assesses data on respiratory symptoms, allergy, housing, smoking habits of the parents, medical survey and control, hospitalisation rate, medication, and allergy symptoms among first degree family members. The main respiratory symptoms assessed were: cough, wheeze, dyspnea during exercise, dyspnea at night, and asthma attacks. Symptoms were scored positive as follows: cough, if the patient regularly coughed at least 3 months of the past year, wheeze, if wheezing or whistling sounds were heard in the chest, without having a cold, at least on 3 occasions during the past year, exercise-induced dyspnea, if the patients frequently experienced shortness of breath during physical exertion, dyspnea at night, if the patient frequently awoke at night because of shortness of breath. PBW was scored positive if a patient from the bronchiolitis group suffered from one or more of these items and/or if they were seen by a doctor for respiratory complaints during the first year of life. Asthma was scored positive if a patient suffered from one of these items during the year before the interview was done. Asthma attacks were scored positive if the patient had episodes of breathlessness with wheezing during the year before the interview was performed, verified by a doctor.

Atopy was scored positive if a patient suffered from frequent periods of coughing, wheezing, dyspnea, running nose or sneezing occurring in relation to, or after exposure to trees, grass, flowers or plants in spring and/or summer, house dust, animals or feathers. Family atopy was scored positive if a first line relative suffered from asthma or bronchitis, hay fever, eczema, or food allergy. Dust exposure was scored positive if there was fixed floorcovering or carpets and curtains and upholstered furniture in the living room and/or the sleeping room of the patient.

For the power analysis to estimate our sample size we mainly focused on the short-term arm of our study, in which 54 patients were included (27 in each treatment group). Based on previous reports we expected a frequency of PBW of 75%. At a significance level of 0.05, the initial sample size of 54 patients would still provide 90% power to detect a decrease in PBW of 40%.

Statistical analysis
Statistical analysis was performed with the SPSS package for Windows, version 8.0.0 (SPSS Inc., Chicago, Ill.). For normally distributed data the student's t-test was used to compare group means, otherwise the Mann-Whitney U test was applied. Proportions were compared by the chi-square test. A two-sided p value of <0.05 was considered statistically significant.

Results
During three RSV seasons from December 1992 until January 1995, 54 patients were enrolled into the study, 27 were randomised to receive prednisolone and 27 placebo. Two patients died, one because of respiratory insufficiency during RSV bronchiolitis and one at the age of 1 unrelated to RSV bronchiolitis. Because 5 of the remaining 52 patients could not be traced, 47 patients were available for the follow-up study, of which 24 had received prednisolone and 23 placebo. The 5 patients lost to follow-up behaved not different with regard to disease severity and improvement during the acute phase of RSV bronchiolitis.

According to Martinez et al., children were divided into four groups according to their history of wheezing: those who never wheezed, those who wheezed during the first year of life but had stopped wheezing before the age of 5 (transient wheezing), those who wheezed during the first year of life and had asthma or asthma attacks at the mean age of 5 (persistent wheezing) and finally those that suffered from asthma or asthma attacks at the mean age of 5 but had not wheezed during the first year of life (late-onset wheezing).

There were no statistically significant differences in the demographic characteristics between the 24 patients that received prednisolone and 23 patients that received placebo (Table 6.1).

There were no significant differences in proportions of patients that suffered from transient wheezing (8% vs. 17%), persistent wheezing (42% vs. 31%) or late-onset wheezing (17% vs. 13%) between the prednisolone- and the placebo-treated group (Table 6.2).

Because patients with severe bronchiolitis proved to have most benefit from corticosteroids during the acute phase of RSV bronchiolitis (short-term effect), we also analysed the long-term effect of prednisolone during the acute phase of RSV in this subgroup of patients. Severe bronchiolitis was defined as those patients with a pre-treatment severity score of acute infection of 6 or more (severity score ranges from 0 to 12) and those patients that needed mechanical ventilation. In this subgroup (11 patients in the prednisolone group, 10 patients in the placebo group) the frequencies of transient wheezing, persistent wheezing and late-onset wheezing were also not significantly different between the prednisolone and the placebo group (data not shown).
Discussion
We found that prednisolone during the acute phase of RSV bronchiolitis has no preventive effect on wheezing in the subsequent year, or the development of asthma at the mean age of 5 years.

There is ongoing discussion about whether RSV bronchiolitis is the first manifestation of asthma, in genetically predisposed children, or whether RSV bronchiolitis early in life causes airway responsiveness and subsequently asthma. Results of several studies are supportive for the first theory. Some authors found that atopy and a positive family history for asthma are the risk factors for PBW and bronchial asthma. \(^3,7-9,11\) Welliver et al demonstrated that high levels of RSV specific IgE in nasal secretions during the acute infection are correlated with airway responsiveness later in life. \(^24\) In addition, a reduced lung function already exists before the first RSV infection in infancy, a finding that is also supportive for the theory that some children are predisposed for wheezing during RSV infection. \(^12\) However, others could not confirm the role of atopy as a risk factor for airway responsiveness after RSV bronchiolitis. \(^5,6,25-27\) In addition, the results of other studies are more supportive for the theory that direct viral injury of airway epithelium, as well as the immune response may lead to increased airway responsiveness. Both experimental and clinical studies have demonstrated that the direct viral injury of the airway epithelium as well as the immune response during RSV bronchiolitis, may contribute to increased airway responsiveness and bronchoconstriction during and after RSV infection. \(^13,28\)

It has been demonstrated that the immune response leads to clearance of the virus, but also contributes to the pathogenesis of RSV lower respiratory tract infection. \(^14\)

Several inflammatory cells and mediators during the acute infection play a role in this immune injury that may lead to changes in osmolarity of the epithelial lining fluid, loss of epithelial derived relaxant factors as well as exposure and stimulation of cholinergic sensory nerve fibers. This may in turn play a role in the development of increased airway responsiveness and PBW. \(^14\)

Because RSV bronchiolitis is, in part, an immune mediated disease immune modulating drugs like corticosteroids may be effective both in the acute phase and in preventing the development of increased airway responsiveness and, through this, PBW and asthma. The effect of inhaled corticosteroids on the prevalence of PBW has been evaluated in several trials with conflicting results. \(^16-19\) However, inclusion criteria in these studies were different and medication was started when patients had already recovered from the acute infection, \(^18\) or after the acute phase of the RSV infection. \(^19\)

In addition, follow-up of the patients in these studies was limited to 1 year or less. To our knowledge no studies have been published that investigated the long-term effect of oral corticosteroids during the acute phase of RSV bronchiolitis. In an earlier report, we have demonstrated that oral prednisolone may be effective in accelerating clinical recovery in patients with RSV bronchiolitis, especially in patients with severe bronchiolitis. \(^20\) However, in this follow-up study we could not demonstrate an effect of prednisolone on the development of PBW or asthma. In the subgroup of
patients with more severe bronchiolitis, i.e., the patients who proved to have most benefit from prednisolone during the acute RSV infection, prednisolone was not effective in reducing the frequency of PBW and asthma. In some children the first attack of wheezing may be their first presentation of allergic asthma precipitated by RSV instead of classic bronchiolitis. However, since the presence of atopy is equally divided between the prednisolone- and the placebo-treated group (21% vs. 26%), we believe this is not a major confounding factor in this study.

Since we observed a beneficial effect in the acute phase of the disease of prednisolone, but no effect on the long-term outcome our finding may provide indirect evidence that genetic factors or the direct viral injury may be of more importance in the development of increased airway responsiveness after RSV bronchiolitis than the airway damage due to inflammation.

There are limitations to our study that justify some reservation in the interpretation of the results. First, the number of patients in our study was small. The sample size was mainly based on a power analysis for the short-term study. Nevertheless, we calculated that with the initial sample size of 54 patients still with enough power to detect a clinical relevant reduction in PBW of 40%.

A second limitation of our study is the use of questionnaires. Although questionnaires as a tool for investigation of airway symptoms is widely used and accepted, its retrospective use has limitations, such as recall bias. However, our primary question was to evaluate the long-term effect of prednisolone during the acute phase of RSV bronchiolitis. The effect of recall bias on this question is minimised through the double-blind placebo-controlled design.

In conclusion, we found that oral prednisolone during the acute phase of RSV bronchiolitis in infants and young children is not effective in preventing post-bronchiolitic wheezing in the first year after bronchiolitis or asthma at the age of 5 years.
Table 6.1
Demographic characteristics of the study groups.

<table>
<thead>
<tr>
<th></th>
<th>Prednisolone n=24</th>
<th>Placebo n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endogenous factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, yrs (s.e.m.)</td>
<td>4.9 (0.13)</td>
<td>5.1 (0.16)</td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Atopy</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Family history for atopy</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Pre-existing morbidity*</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><strong>Exogenous factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals in house</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Maternal smoking in pregnancy</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Smoke exposure after birth*</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Dust exposure</td>
<td>18</td>
<td>12</td>
</tr>
</tbody>
</table>

* None of the differences between the 2 groups was statistically significant
# Prematurity and/or chronic lung disease of infancy, or heart disease
* One or more persons smoking in the household

Table 6.2
Airway symptoms in bronchiolitis patients who received prednisolone or placebo.

<table>
<thead>
<tr>
<th></th>
<th>Prednisolone n=24</th>
<th>Placebo n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>No wheezing</td>
<td>8 (33%)</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Transient wheezing</td>
<td>2 (8%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Persistent wheezing</td>
<td>10 (42%)</td>
<td>7 (31%)</td>
</tr>
<tr>
<td>Late onset wheezing</td>
<td>4 (17%)</td>
<td>3 (13%)</td>
</tr>
</tbody>
</table>

* None of the differences between the 2 groups was statistically significant
References


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