Risk factors for the development of bronchiolitis obliterans in children with bronchiolitis

A J Colom, A M Teper, W M Vollmer, G B Diette

**Background:** Bronchiolitis obliterans (BO) is an uncommon and severe form of chronic obstructive lung disease in children that results from an insult to the lower respiratory tract.

**Methods:** A case-control study of children under the age of 3 years was performed in 109 cases and 99 controls to determine risk factors for the development of BO. Participants were evaluated by immunofluorescence viral tests, pulmonary function tests, and questions to assess tobacco and other exposures.

**Results:** Bronchiolitis due to adenovirus (odds ratio (OR) 49, 95% confidence interval (CI) 12 to 199) and the need for mechanical ventilation (OR 11, 95% CI 2.6 to 45) were strongly and independently associated with an increased risk for BO. Factors not associated with post-infectious BO included age of the child, sex, and environmental tobacco exposure (either in utero or during infancy).

**Conclusions:** Adenovirus infection and need for mechanical ventilation are significant risk factors for developing BO in children. Further research is needed to determine why these risk factors are so strong and how they may contribute to the development of the disease.
measurements were done according to the ATS/ERS guidelines. Values of maximal flow at functional residual capacity ($V'_{\text{max}}$FRC) were expressed as $Z$ scores. Data on current exposure to environmental tobacco smoke (ETS) and exposure to ETS during pregnancy were obtained from the medical records or from interviews with the parents.

**Statistical analysis**

Assuming that 10% of the control subjects would have had exposure to AV, the study had 80% power to detect a 16% difference in AV exposure probabilities between cases and controls. Risk factors were assessed using logistic regression analysis and the results are reported as odds ratios (OR) with 95% confidence intervals (CI). Interaction terms were used to test for lack of additivity of effects on the ln(odds) scale. The following variables were considered as potential risk factors for post-infectious BO: sex, prenatal and postnatal ETS exposure, age at admission for bronchiolitis, evidence of specific viral aetiologies for the bronchiolitis, and the need for mechanical ventilation during the target admission. The 6 month age cut off was used because 67% of the patients were younger than 6 months.

Analyses were performed using Stata for Windows (Stata Corp, College Station, TX, USA) and Epi-Info (US Department of Health and Human Services/Centers for Disease Control and Prevention, Atlanta, USA) statistical software packages. A $p$ value of $<0.05$ indicated statistical significance.

**RESULTS**

Participants ranged in age from 1 to 26 months at the time of their initial admission for bronchiolitis, with a mean age of 6 months among cases and 5 months among controls (table 1); 60% of cases and 58% of controls were boys. The number of new cases of post-infectious BO during the period of the study showed substantial variation from year to year (fig 1). Almost all (98%) of the controls were admitted in the fall or winter compared with 75% of patients with post-infectious BO. In those post-infectious BO patients tested, AV was detected in 72%, RSV in 10%, parainfluenza in 4%, and influenza in 1%. In control patients, RSV was the virus most frequently identified (58%), and only 3% were positive for AV. 34% of patients with post-infectious BO required mechanical ventilation compared with only 3% of patients in the control group. The median stay in hospital was 30 days (range 11–120) in post-infectious BO patients and 6 days (range 1–40) in controls.

In bivariate analyses AV infection (OR 83, 95% CI 22 to 441) and the need for mechanical ventilation (OR 12, 95% CI 5 to 34) were exceptionally strong risk factors (table 1), and persisted as significant predictors of risk for post-infectious BO in multivariate logistic regression models (table 2). A formal test for interaction in the logistic model was not significant.

**Clinical findings**

Chest radiography and PFTs were performed at the time of the clinical evaluation of the post-infectious BO cases, which occurred a mean of 4 months after the onset of illness (range 5–30). Patients with BO had high respiratory rates (mean 37 breaths/min, range 35–40); 70% (56/80) had a rigid thorax, 74% (69/93) had wheeze, and 89% (81/91) had persistent productive cough. Oxygen saturation was lower than normal (mean (SD) $\text{SaO}_2$ 92 (5)%). Most children were not malnourished (mean (SD) $Z$ score length for age $-1.6$ (1), weight for length $-0.45$ (1)).

Chest radiographs from 98 of the patients with post-infectious BO showed air trapping (96%), atelectasis (75%), areas with an increased interstitial pattern (55%), and honeycombing (34%). The most frequent findings on the HRCT scans (reported for 62 of the cases) were mosaic perfusion (60%), bronchiectasis (58%), and atelectasis (44%).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ($&lt;6$ $\leq 6$ months)</td>
<td>1.4</td>
<td>0.4 to 5.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.8</td>
<td>0.2 to 2.6</td>
<td>0.7</td>
</tr>
<tr>
<td>ETS at present</td>
<td>1.4</td>
<td>0.4 to 4.5</td>
<td>0.5</td>
</tr>
<tr>
<td>ETS during pregnancy</td>
<td>0.4</td>
<td>0.1 to 3.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Adenovirus infection</td>
<td>49</td>
<td>12 to 199</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>11</td>
<td>2.6 to 45</td>
<td>0.001</td>
</tr>
</tbody>
</table>

ETS, environmental tobacco smoke.
suggest that a specific immunological response may be important in the development of BO following AV infection. In the present study, illness occurred in very young infants—67% were younger than 6 months and 93% were younger than 12 months—but our findings did not show that age was a risk factor for developing post-infectious BO. In previous studies patients admitted with bronchiolitis and malnutrition had a more severe course; however, malnutrition was not an important factor in the present study as most of the children were not malnourished.

Although AV was identified in most of the post-infectious BO patients at the onset of the illness, other viruses were also found. RSV is the most frequent casual agent of bronchiolitis and occurs mainly during winter months. An association between BO and RSV has been reported only rarely, and the pathogenesis of BO is not clear in these patients. Simultaneous infections of RSV and AV have also been reported.

In these cases it would seem most likely that the AV infection is the cause of BO. About one quarter of the total diagnosed cases infected with influenza develop complications, mostly in younger children (0–4 years of age). However, BO is a rare complication of influenza with only a few cases reported in infancy and early childhood.

The use of mechanical ventilation, an important treatment for children in intensive care units, has apparently allowed severely ill children to survive who previously would have died before BO could be recognised. Mechanical ventilation is indispensable for the support of critically ill patients with respiratory insufficiency. Although our study found that mechanical ventilation was a significant risk factor for post-infectious BO, our results do not indicate whether it causes injury to the lung that increases the risk for developing post-infectious BO or whether it merely serves as an indicator of severity of illness. Mechanisms by which mechanical ventilation could cause lung injury include untoward effects from volutrauma, oxygen toxic effects, and barotrauma.

Further research is needed to clarify the relationship between mechanical ventilation and post-infectious BO, and to study whether lung protective strategies are needed for this vulnerable population. Cidofovir, a new antiviral agent is under investigation and strategies are needed for this vulnerable population.

The ethnic background of patients is another factor that has been linked with the risk for developing post-infectious BO. Two ethnic indigenous populations of children in New Zealand and central Canada have been reported to be particularly susceptible to developing post-infectious BO, which suggests that genetic factors may be important.

Our study evaluated children of different geographical origins but did not assess ethnicity. The relationship of post-infectious BO to race/ethnicity is an interesting and important topic for future research.

All tested patients with post-infectious BO had a V′maxFRC that was more severely affected than in other diseases such as bronchopulmonary dysplasia or asthma which, even in their most severe forms, usually respond to bronchodilators. This finding confirms our previous report about the use of PFTs which enable us to improve the diagnostic approach to post-infectious BO. We believe that the patient’s clinical history and the radiological and HRCT images are sufficient in most cases to confirm the diagnosis and to differentiate post-infectious BO from other pulmonary disorders. These clinical evaluations should be considered in tandem with the functional pattern which, in post-infectious BO, is characterised by severe and fixed obstruction, an increase in resistance, and a decrease in lung compliance. In the few cases in which doubt persists about the diagnosis, a lung biopsy may be needed.
We conclude that both AV infection and mechanical ventilation are strongly associated with the development of post-infectious BO. The immunological response of the host and genetically determined factors could be additional factors that modify or increase susceptibility to the condition. Strategies to prevent infection with AV, such as development of a vaccine, should be encouraged to prevent this devastating illness. In the meantime, early recognition is vital so that children can be isolated to prevent the spread of infection to others. When AV is suspected or isolated, early aggressive treatment is warranted, and future clinical studies are required to determine the best treatment strategies.

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REFERENCES
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