

persistent inflammation in bronchial biopsy specimens, while the number of sputum neutrophils and lymphocytes and the levels of interleukin-8 and eosinophilic cationic protein actually increased at 1 year. The duration of smoking cessation is also important because, with a longer duration, the CD8 cell numbers decrease, plasma cell numbers increase, while other inflammatory cells persist.<sup>14</sup> Since oxidative stress (as reflected in protein carbonyl levels) also persists after smoking cessation, the relationship between oxidative stress, duration of cessation, and inflammatory markers needs further study.

There has been renewed interest in obstructive lung disease in the elderly. This population is at an increased risk of both pulmonary and systemic injury from tobacco smoke. The Health Aging and Body Composition study is a prospective cohort of individuals aged 70–79 years. In well functioning elderly subjects with or without obstructive lung disease, interleukin-6 is associated with reduced FEV<sub>1</sub>, quadriceps strength, and exercise capacity.<sup>15</sup> The findings of Nagai *et al* add the possibility that increasing oxidative stress with age may also contribute.

Perhaps the finding that oxidative stress increases with age is not too surprising. Older smokers are exposed to cigarette smoke over many years. Even in a healthy volunteer population, neutrophil counts in induced sputum increased with age,<sup>16</sup> possibly as a result of exposure to pollutants. Smoking leads to age related decreases in antioxidant activity in alveolar

macrophages. There have been few attempts at targeting oxidative stress via supplementing antioxidants or boosting endogenous levels in the older smoker, but this certainly should be evaluated. As already mentioned, the benefits of smoking cessation can be seen regardless of age and include a decreased rate of decline in FEV<sub>1</sub>, a lower risk of stroke or myocardial infarction, and meaningful life extension. Surprisingly, the elderly are less likely to receive smoking cessation advice than their younger counterparts.<sup>17</sup> Clearly, as more research is performed on pathogenetic mechanisms such as oxidative stress in the elderly smoker, simultaneous attention must be paid to prevention.

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Post-infectious bronchiolitis obliterans in children

## Insights into post-infectious bronchiolitis obliterans in children

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New information contributing to our understanding of risk factors predisposing to bronchiolitis obliterans in children

**B**ronchiolitis obliterans (BO) is a rare form of chronic obstructive lung disease that follows an insult to the lower respiratory tract.<sup>1</sup> It is characterised by inflammation and fibrosis of the terminal and respiratory bronchioles that lead to narrowing and/or complete obliteration of the airway lumen. Pathologically, two forms of BO

are recognised, and these may be part of a continuum. Proliferative bronchiolitis is characterised by intraluminal exudates, whereas constrictive bronchiolitis is characterised by alterations in the walls of the bronchioles ranging from inflammation to fibrosis and, ultimately, to complete obliteration of the lumen.<sup>2</sup> The histological findings of

constrictive bronchiolitis are a common end point for many disorders that are associated with airway epithelial injury including allograft recipients (lung, heart-lung, and bone marrow), previous lower respiratory tract infection (adenovirus,<sup>3–6</sup> influenza,<sup>7</sup> parainfluenza, measles, respiratory syncytial virus,<sup>8</sup> or *Mycoplasma pneumoniae*<sup>9–11</sup>), collagen vascular disease (especially rheumatoid arthritis and Sjogren's syndrome), toxic fume inhalation, chronic hypersensitivity pneumonitis, drugs (such as penicillamine or cocaine), and Stevens-Johnson syndrome.<sup>12–13</sup> With the exception of specialised centres where large numbers of paediatric lung, heart-lung, or bone marrow transplants are performed, post-infectious BO is generally the most common form of BO in children worldwide.

For unclear reasons, post-infectious BO seems to occur more frequently in the southern hemisphere (Argentina,

Chile, New Zealand, and Australia), but it is also found in other parts of the world. Genetic factors may play a role in that the prevalence of BO appears to be increased in Native Americans in Canada,<sup>14,15</sup> Polynesians in New Zealand,<sup>16</sup> and Native Koreans.<sup>11</sup> A recent study found that HLA-DQB1\*0302, an antigen highly represented in Amerindians, was increased in children with BO in Argentina.<sup>17</sup>

In this issue of *Thorax* Colom *et al*<sup>18</sup> present the first systematic study examining the risk factors associated with the development of BO in children. Given the relatively high incidence of BO in Argentina, the authors have accumulated extensive experience with this disorder and have a unique opportunity to study this relatively rare disease. Although the association between adenovirus infection and BO in children has been well recognised,<sup>4,11,15</sup> this study convincingly shows that adenovirus is by far the most common cause of post-infectious BO. The additional finding that mechanical ventilation is an independent risk factor for the development of BO is not surprising, but this association has never been previously examined. The authors are careful to point out that their data do not allow them to determine whether mechanical ventilation contributes to the development of BO or simply reflects the severity of the acute insult. This paper therefore presents important new information that contributes to our understanding of risk factors predisposing to BO in children.

Formally evaluating this rare disease is problematic for many reasons. Most importantly, perhaps, is that no single classification scheme has been widely accepted. Pathological,<sup>2</sup> clinical,<sup>19,20</sup> and radiological<sup>21</sup> classification schemes have been proposed, mainly for BO in adults. Although the histopathological subtypes can be classified by the pathologists, the clinical and radiological correlates are not always obvious. Furthermore, even though histopathology is considered the gold standard for diagnosis, the non-homogenous distribution of pathology in the affected lung can lead to sampling error when attempting to diagnose BO by biopsy.<sup>22,23</sup> Thus, definitively diagnosing this disorder remains problematic, even with lung biopsy. In this study the authors chose to define BO using clinical criteria that they had used previously to describe the clinical signs and symptoms associated with chronic pulmonary disease following severe adenoviral illness in children.<sup>3</sup> Using infant lung function techniques, they found that these young children had severe fixed bronchial obstruction,

decreased pulmonary distensibility, and increased airway resistance. They concluded that their findings might represent the functional expression of the histopathological damage of BO. Since lung biopsies are often non-diagnostic in BO and carry risks, the clinical definition developed by the authors, although imperfect, seems appropriate to identify the cohort of children who developed severe post-infectious obstructive lung disease in the current study.

Although not a primary focus of this study, one additional interesting and important observation was the excellent long term outcome of the patients with BO. This finding supports the impression of many of us that post-infectious BO in children carries a better prognosis than other forms of BO, particularly those that occur in adults. Given the limitations of its retrospective design, this study represents a good first step in the systematic evaluation of children with BO. Whether these findings can be extrapolated to BO in other parts of the world remains to be seen.

Further research is needed to ascertain the mechanisms by which adenovirus—more than other respiratory pathogens—contributes to the development of BO. Additional investigations should be done to define more clearly the specific value of clinical presentation, pulmonary function testing, high resolution computed tomography, and lung biopsy in the diagnosis of BO in children. Surrogate markers of disease activity need to be developed. For example, preliminary studies suggest that KL-6, a protein expressed by activated pulmonary epithelial cells, is increased in the serum of lung transplant patients who develop BO.<sup>24</sup> Whether KL-6 would be a useful marker in post-infectious BO should be evaluated. Finally, systematic studies are needed to determine if treatments such as infliximab<sup>25</sup> and azithromycin,<sup>26</sup> suggested for other forms of BO, are effective in improving the outcome of patients with post-infectious BO.

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