Bronchiolitis obliterans in children

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Current Opinion in Pediatrics 2008, 20:272–278

Purpose of review

In this review, we discuss recent advances in our understanding of the etiology, pathology and pathogenesis, clinical presentation, diagnosis, treatment, and outcome of bronchiolitis obliterans in the nontransplant, pediatric population.

Recent findings

The diagnosis of bronchiolitis obliterans in children can be made with confidence based on clinical presentation, particularly with a history of adenovirus bronchiolitis or pneumonia, fixed obstructive lung disease on pulmonary function testing, and characteristic changes of mosaic perfusion, vascular attenuation, and central bronchiectasis on chest high-resolution computed tomography, thus avoiding the need for lung biopsy in most patients. Patients with postinfectious bronchiolitis obliterans generally have chronic, nonprogressive disease; in contrast, patients with bronchiolitis obliterans from Stevens–Johnson syndrome often have progressive disease that may require lung transplantation.

Summary

Bronchiolitis obliterans is a rare form of chronic obstructive lung disease that follows a severe insult to the lower respiratory tract, resulting in fibrosis of the small airways. In the nontransplant pediatric population, adenovirus infection is the most common cause. Treatment is largely supportive and prognosis is mainly related to the underlying cause and to the severity of the initial insult.

Keywords

adenovirus, bronchiolitis obliterans, children, high-resolution computed tomography, obstructive lung disease, Stevens–Johnson syndrome

Curr Opin Pediatr 20:272–278

1040-8703

Introduction

Bronchiolitis obliterans is a rare, fibrosing form of chronic obstructive lung disease that follows a severe insult to the lower respiratory tract and results in narrowing and/or complete obliteration of the small airways [1]. Although bronchiolitis obliterans has been described in all age groups, the frequency of underlying causes and potential prognoses are different for children and adults. For example, bronchiolitis obliterans in children is most often seen following a severe lower-respiratory-tract infection, usually of adenovirus [2,3•], whereas bronchiolitis obliterans in adults is more commonly associated with occupational inhalation injuries, hypersensitivity pneumonitis, and autoimmune disorders [4]. As bronchiolitis obliterans has been extensively studied as a well-defined complication of lung, heart/lung, and bone marrow transplantation, we will focus on pediatric bronchiolitis obliterans in the nontransplant population and review the most recent advances in our understanding of the etiology, pathology and pathogenesis, clinical presentation, diagnosis, treatment, and outcome.

Etiology

Table 1 summarizes the known causes of and conditions associated with bronchiolitis obliterans. In up to one-third of cases, the cause is unknown [5].

In the nontransplant population, the most common form of bronchiolitis obliterans in children follows a severe lower-respiratory-tract infection. Although several authorities have suggested that postinfectious bronchiolitis obliterans is more common in the southern hemisphere, particularly in New Zealand and South American countries such as Argentina, Brazil, Chile, and Uruguay [6], bronchiolitis obliterans has been reported in Canada [7], the USA [8], Turkey [9], South Korea [5], and Taiwan [10]. People of Asian descent appear to be most susceptible, as bronchiolitis obliterans has been described in Polynesians in New Zealand, Metis and Native Americans in Canada, South Koreans, and Taiwanese. A recent study from Argentina reported that children who developed postinfectious bronchiolitis obliterans had an increased frequency of HLA haplotype DR8-DQB1*0302, an allele highly

Table 1 Etiology of bronchiolitis obliterans

Postinfectious	Adenovirus types 3, 7, and 21
	Influenza
	Parainfluenza
	Measles
	Respiratory syncytial virus (RSV)
	Varicella
	Mycoplasma pneumoniae
Posttransplant	Chronic rejection of lung or heart/lung transplantation
	Graft-versus-host disease associated with bone marrow transplantation
Connective tissue disease	Rheumatoid arthritis
	Sjogren's syndrome
	Systemic lupus erythematosus
Toxic fume inhalation	NO_2
	NH_3
Chronic hypersensitivity pneumonitis	Avian antigens
	Mold
Aspiration	Stomach contents: gastroesophageal reflux
	Foreign bodies
Drugs	Penicillamine
	Cocaine
Stevens–Johnson syndrome	Idiopathic
	Drug-induced
	Infection-related

represented in the Amerindian population, providing a possible explanation for the high frequency of bronchiolitis obliterans in South American countries [11].

Adenovirus has been documented as the leading infectious cause of bronchiolitis obliterans worldwide. Colom *et al.* [2] recently published the largest case–control study to date, with 109 cases and 99 controls, over 12 years, at the Children's Hospital in Buenos Aires, Argentina. Adenovirus infection was identified in 71% of patients with postinfectious bronchiolitis obliterans and was found to be a strong independent risk factor for the development of postinfectious bronchiolitis obliterans (odds ratio 49, 95% confidence interval 12–199, $P < 0.001$). Although adenovirus tended to affect young infants more, age was not found to be a statistically significant risk factor. The severity of the acute illness seemed to correlate with development of bronchiolitis obliterans, with bronchiolitis obliterans patients requiring mechanical ventilation more often (34 versus 3%) and much longer lengths of stay in the hospital (30 versus 6 days) when compared to controls. Mechanical ventilation was found to be a significant independent risk factor (odds ratio 11, 95% confidence interval 2.6–45, $P = 0.001$), although it was unclear whether it contributed to the development of bronchiolitis obliterans through lung injury or merely served as an indicator of the severity of the illness.

Castro-Rodriguez *et al.* [12] recently examined the relationship between adenovirus and the development of bronchiolitis obliterans prospectively, assessing 45 infants with adenovirus pneumonia during an epidemic outbreak and following them for 5 years with pulmonary function testing and high-resolution computed tomography (HRCT). Similar to the Colom *et al.* study [2], they found that during the acute adenovirus pneumonia, the children who eventually developed bronchiolitis obliterans had more severe respiratory compromise, indicated by more accessory muscle use and crackles, hospital days, intensive care unit admission, mechanical ventilation, oxygen use, and corticosteroids and β-2 agonist administration. Laboratory differences were generally negligible, but patients who developed bronchiolitis obliterans did tend to have more atelectasis on chest X-ray. During the 5-year follow-up period, almost half of the cohort (47.4%) developed bronchiolitis obliterans, and those patients were more likely to require home oxygen therapy, develop recurrent pneumonia and severe wheezing episodes, and demonstrate chronic or changing atelectasis on chest radiographs compared to those who did not develop bronchiolitis obliterans.

Less common infectious causes of bronchiolitis obliterans are respiratory syncytial virus (RSV), measles, influenza, parainfluenza and *Mycoplasma pneumoniae*. Although some are skeptical, Chan *et al.* [13] and Lobo *et al.* [14] identified RSV as the causal agent in 3/14 cases and 3/10 cases, respectively. Yalcin *et al.* [9] suggested that a co-infection with another organism might contribute to the development of bronchiolitis obliterans in patients with RSV infection.

A particularly severe and often progressive form of bronchiolitis obliterans has become increasingly recognized as a complication of Stevens–Johnson syndrome (SJS). Although the mechanisms are poorly understood, authorities propose that bronchiolitis obliterans occurs as a result of the primary lesions of SJS in the respiratory tract, secondary pulmonary infection, or a Type III immune mechanism. In a recent report of two cases, Bakirtas *et al.* [15•] described one patient who developed bronchiolitis obliterans during the acute phase 15 days after onset of SJS, while the other developed bronchiolitis obliterans in the convalescent stage 5 months after SJS diagnosis. Both patients were diagnosed without lung biopsy, and one patient showed significant bronchodilator responsiveness on pulmonary function testing.

Pathology and pathogenesis

Bronchiolitis obliterans is characterized by partial or complete occlusion of the lumens of terminal and respiratory bronchioles by inflammatory and fibrous tissue [1]. The histologic findings represent a common endpoint for many disorders that insult the epithelium of the small airways with subsequent intraluminal scarring rather than normal repair.

The initial insult to the small airways results in derangements in epithelial cell function or local necrosis. An intraluminal fibrinopurulent exudate accumulates and induces the deposition of collagen and mucopolysaccharides from myofibroblasts. In some cases, a large intraluminal polyp, known as a Masson body, may develop from the proliferation of histiocytes and capillaries. These lesions may progress to eventually form the near-circumferential scarring typical of severe bronchiolitis obliterans. Gradual resorption of the fibrovascular connective tissue is possible with restoration of normal airway caliber and epithelium, but acute inflammation of the airway epithelium can induce continued deposition of collagen between the smooth muscle and lamina propria of the airway wall, encroaching on the airway lumen.

Myers and Colby [16] proposed bronchiolitis obliterans could be divided pathologically into two major categories that may be part of a continuum. The first, proliferative bronchiolitis obliterans, also called pure-type bronchiolitis obliterans, is characterized by obstruction of airway lumen by polyps of granulation tissue. When this granulation tissue extends into the alveoli, the lesion is called bronchiolitis obliterans with organizing pneumonia, now known as cryptogenic organizing pneumonia. The second and much more common type, constrictive bronchiolitis, is characterized by alterations in the walls of the bronchioles ranging from inflammation to fibrosis and, ultimately, to complete obliteration of the airway. A rat model, utilizing tracheal instillation of nitric oxide, has been developed that simulates the proliferative and constrictive airways lesions of bronchiolitis obliterans [17]. This model may be suitable for further study into the pathogenesis and treatment of bronchiolitis obliterans.

In a series of 37 patients, Mauad and Dohlnikoff [6] found 97% of childhood bronchiolitis obliterans to be the constrictive type, with variable degrees of airway obstruction. Indirect signs of obstruction, such as macrophage accumulation, bronchiectasis, mucostasis, and hyperinflation, were always present.

In addition to small-airways involvement, abnormalities can also be seen in the large and medium-sized airways with hypertrophy or thickening of the bronchial epithelium. Bronchiectasis develops in the more severely affected airways with cellular infiltration of the wall extending to the peribronchial space, destruction and disorganization of the muscle and elastic tissue of the wall, and fibrosis of the wall. Occasionally, fibrous membranes occlude the lumens of major bronchial branches resulting in bronchitis obliterans.

Patients with severe adenovirus pneumonia have been shown to have immune complexes containing adenovirus antigen in the lung along with increased levels of interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α). A recent study by Koh *et al.* [18•] showed increased levels of neutrophils and IL-8 that correlated with each other in bronchoalveolar lavage (BAL) fluid from patients with bronchiolitis obliterans following measles, suggesting a role for IL-8 as a chemoattractant and activator of neutrophils. In addition, the authors reported increased levels of $CD8^+$ T-cells, suggesting a role for T-lymphocytic inflammation in the pathogenesis of bronchiolitis obliterans.

Clinical presentation

The initial presentation of infants and children who develop postinfectious bronchiolitis obliterans is often similar to that of an acute episode of severe viral bronchiolitis with the exception of less prominent rhinorrhea. Infants are initially ill with fever and cough and subsequently develop dyspnea and wheezing. Some infants and children present more severely with pneumonia and respiratory failure from adenovirus or other infectious agent. Regardless of etiology, the development of bronchiolitis obliterans is characterized by tachypnea, increased antero-posterior chest diameter, crackles, wheezing, and hypoxemia that persists for at least 60 days after the initial lung injury. The clinical and radiographic features of bronchiolitis obliterans may wax and wane for weeks or months, with recurrent episodes of atelectasis, pneumonia, and wheezing, and incomplete recovery.

Diagnosis

A comprehensive approach utilizing a combination of history and physical exam, infectious-disease evaluation, imaging studies, pulmonary function tests, and occasionally lung biopsy is essential to arriving at the correct diagnosis.

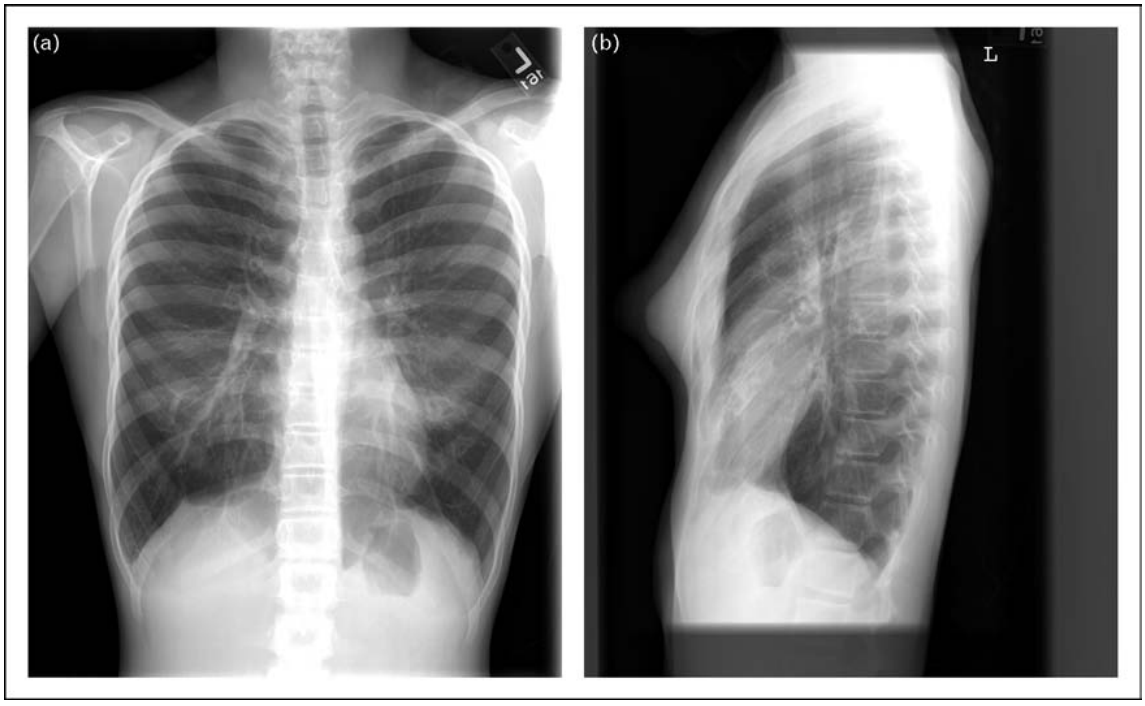
Infectious-disease evaluation

As adenovirus has been clearly established as a risk factor for bronchiolitis obliterans, obtaining appropriate viral cultures, rapid tests by immunoflourescence or radioimmunoassay, paired serology, and DNA probes for adenovirus, as well as other viruses, during the acute illness can be very valuable. Although chronic adenoviral infection has been occasionally identified in children with bronchiolitis obliterans, active adenoviral infection typically resolves following the acute phase of illness in most patients. Identification of *Mycoplasma* through culture, PCR, and serology during the acute illness can also be helpful.

Diagnostic imaging

Classically, chest radiographs show bilateral interstitial prominence and marked hyperinflation (Fig. 1). Up to

Figure 1 Chest radiographs of an 11-year-old female with postinfectious bronchiolitis obliterans



The postero-anterior (a) and lateral (b) views show increased peribronchial thickening and marked hyperinflation.

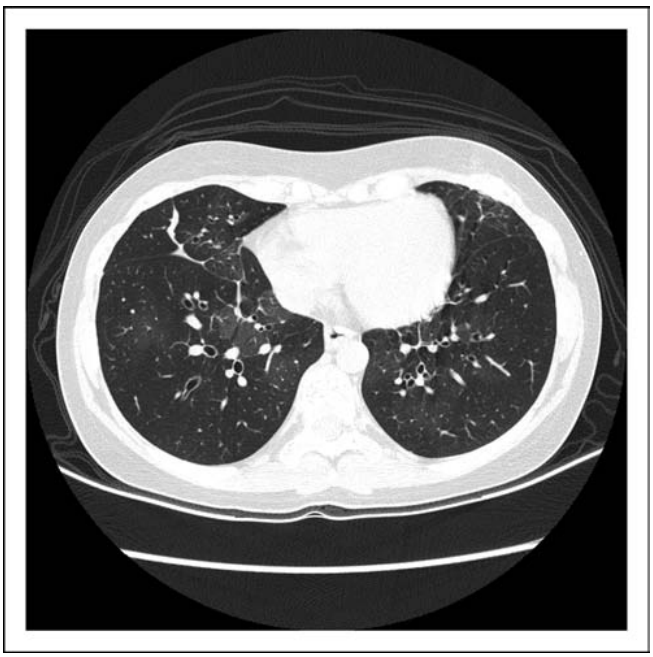
one-third of children with postinfectious bronchiolitis obliterans develop a unique condition known as Swyer–James syndrome, which is characterized by a unilateral, small hyperlucent lung [5]. In addition, many patients develop patchy areas of consolidation or atelectasis. In 10 patients with bronchiolitis obliterans, Chiu *et al.* [3•] found 40% of the patients had patchy consolidation and focal atelectasis on initial imaging in contrast to the usually unremarkable radiographs of patients with classical viral bronchiolitis. Moreover, children with segmental atelectasis/collapse often developed bronchiectasis later.

HRCT of the chest has become an important tool in the diagnosis of bronchiolitis obliterans. The findings of mosaic perfusion, vascular attenuation and central bronchiectasis are diagnostic features of bronchiolitis obliterans (Fig. 2). Kim *et al.* [5] reported that these features were present in 29 of 30 children with bronchiolitis obliterans. Our experience is that these HRCT findings are highly specific but less sensitive for biopsy-confirmed bronchiolitis obliterans in the pediatric, non-transplant population (K.J. Smith *et al.*, unpublished data).

Pulmonary function testing

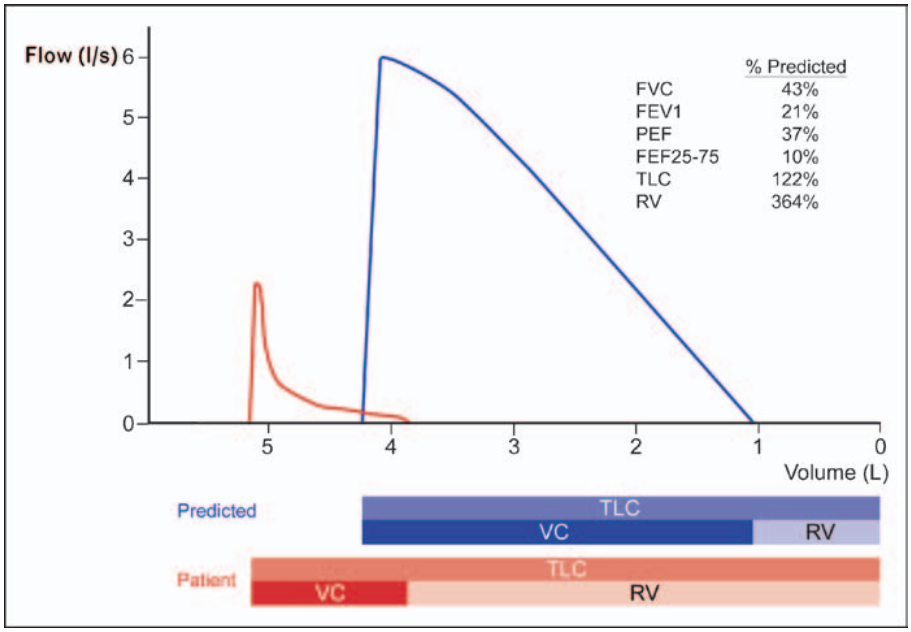
Pulmonary function testing in infants with postinfectious bronchiolitis obliterans typically shows severe fixed airflow obstruction, decreased compliance, and increased resistance with a small response to bronchodilator [2]. Spirometry in older children with bronchiolitis obliterans

Figure 2 High-resolution computed tomography (HRCT) of the same patient as shown in Fig. 1



HRCT demonstrates characteristic changes of bronchiolitis obliterans, including mosaic perfusion with patchy ground-glass opacities, vascular attenuation, and central bronchiectasis.

Figure 3 Pulmonary function testing in the same patient as shown in Fig. 1



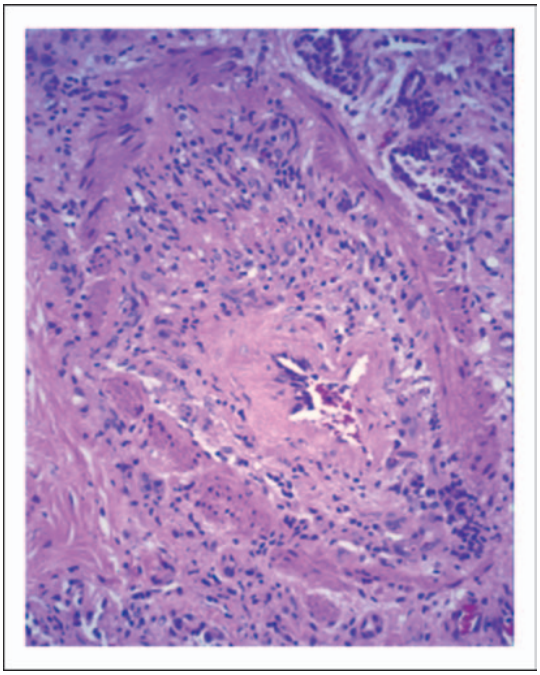
Pulmonary function testing with forced expiratory maneuver and lung volumes in the same patient shows a small, concave loop indicative of severe airflow limitation, hyperinflation (increased TLC), and air trapping (increased RV/TLC). FVC, forced vital capacity; FEF25–75, forced midexpiratory flow; FEV1, forced expiratory volume in 1 s; PEF, peak expiratory flow. RV, residual volume; TLC, total lung capacity.

typically reveals decreased forced expiratory volume in 1 s (FEV1), FEV1/FVC, and peak expiratory flow; a disproportionately marked decrease in forced midexpiratory flow (FEF25–75); and a small, concave expiratory loop, consistent with severe airway obstruction that predominately affects the small airways. Lung volumes typically show an increased total lung capacity and RV/TLC, consistent with hyperinflation and air trapping, respectively (Fig. 3). There may be a small response to bronchodilator.

Lung biopsy

Lung tissue obtained by lung biopsy demonstrating the previously described characteristic airway lesions has been considered the gold standard for diagnosis (Fig. 4). However, the heterogeneous distribution of airway involvement throughout the lung parenchyma can lead to sampling error, reducing the sensitivity [19,20]. In 30 children undergoing lung biopsy for clinically suspected bronchiolitis obliterans, Mauad and Dohlnikoff [6] found histologic changes consistent with bronchiolitis obliterans in 97%, but many of the lesions were mild and did not correlate with the clinical severity of disease. Also, totally obliterated airways were found in only 23% of these children who had open lung biopsies compared to 100% in those who had lobectomy or autopsy. In our experience, lung biopsies may be normal or nondiagnostic in up to one-third of patients. Thus, lung biopsy may not always be

Figure 4 Lung biopsy specimen of the same patient as shown in Fig. 1



This biopsy shows a bronchiole with near-complete obliteration due to prominent subepithelial fibrosis (obliterative bronchiolitis). A peripheral rim of smooth muscle highlights the external diameter of each airway, and a small amount of residual mucosal epithelium highlights the eccentrically positioned severely stenotic lumen. Hematoxylin and eosin, original magnification, 200×. Courtesy of Dr Claire Langston and Dr Megan Dishop, Texas Children's Hospital, Houston, Texas, USA.

diagnostic or may underestimate the severity of the disease process.

Other studies

Ventilation-perfusion lung scans characteristically show patchy areas of severe, matched defects in ventilation and perfusion. However, this technique has been largely replaced by HRCT, which has a much better specificity in diagnosis bronchiolitis obliterans.

Bronchoscopy is occasionally helpful during the acute illness leading to bronchiolitis obliterans by identifying adenovirus or *Mycoplasma* in BAL fluid. Also, bronchoscopy is occasionally helpful in identifying the complete membranous obstruction of subsegmental bronchi in bronchiolitis obliterans.

Thus, in the current era, a diagnosis of bronchiolitis obliterans can be confidently made on the basis of a consistent clinical presentation, the identification of adenovirus or other compatible infectious agent, characteristic HRCT findings, and pulmonary function testing demonstrating fixed obstructive lung disease, supplanting the need for lung biopsy in the majority of cases. Lung biopsy should be reserved for those patients with atypical features of the disease.

Treatment

Important general supportive measures include avoidance of tobacco smoke and other inhaled irritants, annual influenza vaccination, a supervised exercise and fitness program, airway-clearance techniques, adequate nutritional intake, and supplemental oxygen for hypoxemic patients. In patients demonstrating improvement in airway obstruction after bronchodilators, the use of inhaled corticosteroids and bronchodilators is recommended.

Azithromycin, a macrolide antibiotic, has been shown in prospective, double-blind, placebo-controlled trials to be effective in the treatment of diffuse panbronchiolitis and cystic fibrosis, presumably due to anti-inflammatory effects. In addition, several small studies in lung transplant patients with bronchiolitis obliterans syndrome (BOS) have suggested improvement in FEV1 with a prolonged course of oral azithromycin, 250 mg three times per week [21,22]. Although the mechanism is still unclear, Verleden *et al.* [23] were able to show that azithromycin significantly reduced airway neutrophilia and IL-8 mRNA in patients with BOS. Although no studies have been performed in children with postinfectious bronchiolitis obliterans, we believe that oral azithromycin, one dose of 10 mg/kg, given three times weekly, should be used in these patients, based on its proven effectiveness in other chronic obstructive diseases.

Although systemic corticosteroids are frequently used, their effectiveness in improving the outcome of patients with bronchiolitis obliterans is unknown. Although varying degrees of airway inflammation are present in many cases of bronchiolitis obliterans, corticosteroids would not be expected to favorably impact the largely fibrotic component of the disease. If a decision is made to treat, corticosteroids should be given early while the disease process is in the developing phase before airway fibrosis is complete. We prefer pulse steroid therapy, intravenous methylprednisolone, 30 mg/kg (maximum 1 g) infused over 1 h daily, for 3 consecutive days, and repeated monthly, for 3–6 months, as this approach is associated with fewer side effects compared with oral daily or every-other-day corticosteroids. Although also unproven, we believe that immunomodulatory doses of intravenous immunoglobulin (1–2 g/kg) given monthly may be helpful as a steroid-sparing agent in patients with severe disease.

In a single case, Fullmer *et al.* [24] reported the successful use of infliximab, a monoclonal antibody to TNF-α, in reversing the manifestations of bronchiolitis obliterans in a child who had developed this complication following a bone marrow transplant. Whether this therapy would be effective in postinfectious bronchiolitis obliterans remains to be determined. Based on this limited information, the use of anti-TNF-α therapy cannot be recommended at this time, as this therapy can be associated with serious side effects.

Lung transplantation remains the ultimate option for children who have the severe, progressive forms of bronchiolitis obliterans, mainly related to bone marrow or lung transplantation and to SJS. Lung transplantation has been performed on 64 children with various lung disorders at Texas Children's Hospital, over a 5-year period (October 2002–October 2007). The indication for transplant was bronchiolitis obliterans after bone marrow transplant in three children (with two subsequent deaths) and bronchiolitis obliterans after SJS in two (with no deaths to date). Despite the fact that postinfectious bronchiolitis obliterans is far more common that bronchiolitis obliterans related to SJS, no patients with postinfectious bronchiolitis obliterans have been transplanted at our institution.

Outcome

As suggested by our lung transplant experience, those with postinfectious bronchiolitis obliterans tend to have nonprogressive disease in contrast to those with bronchiolitis obliterans following bone marrow or lung transplantation or SJS who often have progressive disease [25]. In general, a more severe initial insult leads to more severe long-term disability. In a prospective

observational study of 31 patients with postinfectious bronchiolitis obliterans, Zhang *et al.* [26] found clinical remission in 22.6%, persistent respiratory signs and symptoms in 67.7%, and death in 9.7%. They also found that older age at onset of illness and presence of atopy, indicated by elevated serum IgE levels, were associated with a worse outcome. In a prospective 5-year follow-up study of 45 children who developed adenovirus pneumonia during an outbreak, Castro-Rodriguez *et al.* [12] reported that 38 survived the acute illness. Eighteen of the survivors developed bronchiolitis obliterans, but although they had more respiratory compromise than survivors without bronchiolitis obliterans, they did not deteriorate during the follow-up period. In a retrospective study of 31 children with bronchiolitis obliterans in Korea and the USA [5], all 25 with postinfectious bronchiolitis obliterans survived. Only one patient with idiopathic bronchiolitis obliterans died, although three patients required lung transplantation, including one with SJS.

Conclusion

Bronchiolitis obliterans is a well-recognized complication of severe lower respiratory tract infection and other insults to the distal airways. With the aid of newer imaging techniques, particularly HRCT, the diagnosis of bronchiolitis obliterans can be made with confidence in patients with a consistent clinical presentation and evidence of fixed airways obstruction by pulmonary function testing, thus avoiding the need for lung biopsy in most cases. Treatment is mainly supportive, as pharmacologic therapy probably does little to reverse the fibrotic airway changes, with lung transplantation reserved for the few patients with severe, progressive disease. Patients with postinfectious bronchiolitis obliterans generally have chronic, but nonprogressive disease and thus the most favorable prognosis.

Acknowledgements

We thank Dr Megan Dishop from the Pathology Department at Texas Children's Hospital for her expert assistance and providing histology photographs for this review.

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 351).

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