Bronchiolitis obliterans: an update

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Purpose of review

Bronchiolitis obliterans (BO) occurs in both post-lung transplant and nontransplant-related individuals, and is characterized by mainly irreversible airflow obstruction that is often ultimately progressive.

Recent findings

While post-lung transplant BO is a major cause of lung allograft dysfunction, and hence is better characterized than nontransplant-related BO, it is likely that many similarities in pathogenesis and treatment apply to both categories.

Summary

Optimal management for BO remains to be established, and the role of retransplantation in this disease requires further consensus. Minimization of risk factors for BO and earlier detection in the form of methacholine challenge testing and HRCT scans of the chest amongst other forms of detection, may help in the stabilization and possible resolution of early BO.

Keywords

bronchiolitis obliterans, transplantation, lung

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Introduction

Bronchiolitis obliterans (BO) describes an inflammatory and fibrogenic process of the membranous and respiratory bronchioles, frequently causing cicatricial luminal narrowing and severe obstructive airways disease. It is synonymous with the term "constrictive bronchiolitis" and should be distinguished from cryptogenic organizing pneumonia/bronchiolitis obliterans organizing pneumonia (COP/BOOP), from which it differs clinically, radiologically, histologically, and in terms of steroid responsiveness [1,2]. Specifically, a patient with a febrile flu-like illness, bilateral crackles on chest auscultation, and patchy infiltrates on a chest radiograph (CXR) may have COP rather than BO, especially if the illness does not respond to antibiotic therapy. Unlike BO, prednisone administration will cure 65 to 85% of such patients with COP because it is a treatable inflammatory lung disease [3]. Further details of the differences between BO and COP have been described elsewhere [2,3].

With regards to BO, this disease entity most frequently occurs in lung and heart-lung allograft recipients [1,4] and is the major limitation to long-term survival after lung transplantation [4]. However, other non-transplant–related etiologies for BO have also been described, and are important to recognize in the appropriate clinical setting. While the pathogenesis of BO is not fully understood, the best-understood form of BO occurs in the post- lung-transplant state. In addition, this latter entity may also serve to help in our understanding of nontransplant-related BO. We therefore review and discuss current concepts of the histopathology, clinical presentation, and diagnosis of both transplant and nontransplant-related BO, and their management.

Histology

Sub-mucosal bronchiolar fibrosis constitutes the histologic hallmark of BO. This is preceded by bronchiolar inflammation resulting in epithelial necrosis [5•], through a process of lymphohistiocytic-mediated cytotoxicity, targeted at the respiratory epithelium. During the initial phase, lymphocytes infiltrate the submucosa of the airways through the basement membrane [6], causing subsequent epithelial cell necrosis with mucosal denudation. A secondary inflammatory cascade occurs in the bronchiolar wall, with the nonspecific release of pro-inflammatory and T-helper 1 (Th1) cytokines and other chemotactic inflammatory mediators that attract various cells, including neutrophils [7•,8]

Accumulation of fibroblasts and myofibroblasts into this endoluminal mix leads to the formation of a polyp of fibromyxoid granulation tissue that obstructs the bronchiole. After subsequent maturation, collagen, the hallmark pathologic lesion of BO, is formed. The collagen may completely obliterate the airway lumen, giving rise to a fibrous scar ("vanishing airways disease") [9], or cause eccentric or concentric endoluminal narrowing [7•]. Elastic stains may reveal residual circumferential elastin around a completely occluded small airway, and aid in its recognition.

When such lesions are accompanied by proliferating fibroblasts and extracellular matrix together with chronic inflammatory cells (lymphocytes, plasma cells, and monocytes), they are considered "active". The bronchiolar infiltrate present in such lesions is both perivascular and transmural, and may cause ulceration of the bronchiolar mucosa (Fig. 1). Conversely, lesions without an accompanying inflammatory cell infiltrate are classified as inactive [10].

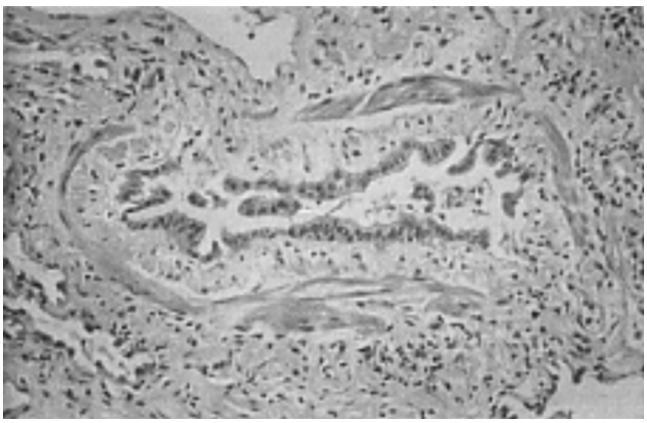
In all cases the lesions are patchy in nature and display temporal heterogeneity with respect to their state of injury [11], and may be accompanied by chronic vascular pathologic changes [12].

Pathogenesis

Bronchiolitis obliterans, posttransplant

Although the exact pathogenesis of posttransplant BO has yet to be fully elucidated, it is probable that it is the end result of a number of repeated insults. These can include ischemia-reperfusion injury to the lung allograft, rejection, infection, and other inflammatory processes that cause airway epithelial tissue damage with a subsequent exaggerated healing response [13]. Of these, it seems in posttransplant BO likely from retrospective epidemiologic analyses that acute cellular rejection is the single most important risk factor for the development of BO [8,14–16]. Heng *et al.* [15] found that three or more episodes of rejection within the first 6 to 12 months after engraftment increased the risk up to four-fold. The degree of rejection may also play a role in the development of BO [17], with increased likelihood of its development in patients with one or more episodes of moderate to severe acute rejection (grade 3 or above) [14]. If acute rejection occurs later posttransplant, the likelihood of BO also appears to be increased [16,18,19]. The development of BO in such lung allografts is very similar in histologic and clinical terms to that seen as a result of graft versus host disease post bone marrow transplantation [20].

Figure 1. Luminal narrowing of bronchiole with active BO showing increased submucosal connective tissue and inflammatory cell infiltrate



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It has also been shown that the presence of lymphocytic bronchiolitis/bronchitis is a likely precursor of BO even in the absence of concurrent acute perivascular rejection or infection [16,21]. Milne *et al.* [22,23] provided further evidence that BO has an immunologic basis, involving T-lymphocytes of suppressor and cytotoxic phenotype.

The development of BO has also been shown to be heralded by an increase in exhaled nitric oxide (NO) levels, primarily from epithelial inducible nitric oxide synthase [24]. Such exhaled NO appears to be reflective of NO levels in the lower airways [25,26]. However, other authors [27,28] reported a variable association between exhaled NO and bronchiolitis obliterans syndrome (BOS), the latter being defined by pulmonary function changes rather than by histology [7•]. The utility of exhaled NO as a marker of inflammation in COPD, asthma, cystic fibrosis, and other lung diseases and disorders is similarly controversial.

Exhaled NO is linked to bronchoalveolar lavage (BAL) neutrophilia [26]; hence monitoring of inflammatory markers in BAL fluid may help identify patients at risk for developing BO [29]. Scholma *et al.* [30] found that the risk of BO was increased in patients with higher total cell granulocyte and lymphocyte counts, the presence of eosinophilic granulocytes, and higher concentrations of interleukin-6 (IL-6) and IL-8. Indeed, the association between BAL neutrophilia and the development of BO may actually precede the 20% decrease in forced expiratory volume in one second (FEV1), the latter being the criterion for the spirometric diagnosis of BOS [31–33].

Insulin-like growth factor-1 may also serve as an early marker for BO, as manifested by increased levels in BAL fluid post transplant. Charpin *et al.* [34] also concluded that this factor contributed to the fibrotic process in BO.

The development of anti-human leukocyte antigen (HLA) class 1 antibodies also seems to be involved in the pathogenesis of BO, with progressive increase in the

anti-HLA antibodies correlating with loss of pulmonary function [35]. However, HLA matching *per se* and its relation to BO remains controversial [8,10]. There is insufficient evidence to show that the characteristics of both the recipient and donor play a major role [36•], although a recent study by Chalermskulrat *et al.* [37•] suggests that it is the degree of HLA class 1 mismatching between donors and recipients that indeed predisposes the latter to both the development and also the severity of BOS.

Non-alloimmunologic inflammatory conditions such as viral infections and/or ischemic injury can also play a role in the development of BO. Cytomegalovirus (CMV) is known to promote acute rejection by decreasing the immunosuppressive effect of cyclosporine and tacrolimus and by up-regulating expression of HLA antigens on both the epithelial and endothelial cells [8]. A direct relation between CMV and BO is, however, unclear with some retrospective studies suggesting that CMV is a risk factor for the development of BO [19,38,39] and others suggesting that it is not [16,18,40].

Data implicating other infectious agents including non-CMV viruses, fungi, bacteria, and "atypical" respiratory pathogens are few and inconclusive. Girgis *et al.* [18] found an association between BOS and bacterial/fungal pneumonia and *Pneumocystis* pneumonia. Heng *et al.* [15] also reported on an association between BOS and pulmonary infection. In both studies the significance was borderline, with other studies failing to find a significant association [13,41].

Controversy exists as to the role of airway ischemia in the development of BO, with several single-center studies not finding an association [13,18,19,42]. However, others including Bando *et al.* [14], did identify airway ischemia as a risk factor for BOS. The International Society for Heart and Lung Transplantation (ISHLT) registry annual report found that donor age, ischemic time, and their mutual interaction were significantly related to BO at 3 years [43].

Bronchiolitis obliterans, nontransplant related

Bronchiolitis obliterans also occurs in the nontransplant setting, and is due to a number of causes [44] (Table 1). It is a well-described result of the inhalational injury of nitrogen dioxide [5•], smoke [45], cocaine, [46] zinc chloride [47], and viral infections, including respiratory syncytial virus [48]. Kreiss *et al.* [49•] described clinical BO in workers at a microwave popcorn plant, likely due to inhalation of volatile butter-flavoring ingredients. Viral infection *in utero* may also contribute to the development of BO as a congenital anomaly [10]. BO can also occur in other divergent infectious processes such as mycoplasma pneumoniae [50]. Therapeutic radiation [51] and ingestion of a variety of drugs, including d-penicillamine [1] are also noteworthy etiologies. BO has also been described in conjunction with ulcerative colitis [52] and ingestion of the East Asian vegetable Sauropus androgynous [53].

Table 1. Some causes of nontransplant related bronchiolitis obliterans

Connective tissue disorders, especially rheumatoid arthritis
Inhalation injury from nitrogen dioxide, smoke, cocaine, zinc chloride, viruses
Infections such as mycoplasma pneumoniae
Drugs such as d-penicillamine
Radiation
Ulcerative colitis

However, BO is more frequently found in association with connective tissue disorders, especially rheumatoid arthritis [5•,54]. Sweatman *et al.* [55] found that histocompatibility antigens B40 and DR1 were increased in frequency in BO associated with rheumatoid arthritis but not in BO alone, and that in both these subgroups A3 and B5 were absent, suggesting that expression of the latter two antigens may protect against the development of BO.

Clinical presentation

The clinical onset of BO is often insidious and nonspecific, and commonly consists of the gradual development of dyspnea on exertion, often accompanied by a chronic productive cough. Fatigue may also be present [4,8,56]. It may also present in previously stable patients who subsequently develop a syndrome resembling an upper respiratory tract infection and are shown to have an irreversible decline in FEV1 thereafter [10]. A minority of patients with BO may also present acutely as an episode resembling asthmatic bronchitis, with cough, wheeze, and a low-grade fever. The response to oral corticosteroids and bronchodilators is limited to absent under these circumstances [10,56]. A positive methacholine challenge test may also serve as a marker of early disease especially in posttransplant BOS [57].

Despite the different clinical manifestations of BO, Van Den Berg *et al.* [58] showed that patients with BOS had reduced quality of life. These issues were associated with increased restrictions on physical mobility, decreased energy, and also psychological disorders especially anxiety and depression.

Physical examination in the early stages of BO is usually unremarkable but may show physical evidence of hyperinflation. Later on in the disease, end inspiratory crackles and wheezes may be heard on chest auscultation [59].

Though small airways disease is the hallmark of BO, involvement of the large airways is common, with bronchiectasis developing possibly as a result of rejection, infection, or both [10,60]. Colonization of these airways

with bacterial and fungal organisms ensues, leading to increased sputum production and cough in the presence of an immunosuppressed milieu. Such colonization is a hallmark of both posttransplant and nontransplant BO. Paradis [61] showed that 50% of such affected patients had bronchitis or pneumonia, predominantly due to *Pseudomonas* and *Staphylococcus* species, with 8% of patients developing fungal infections, especially *Aspergillus*. Infectious exacerbations with high fever and productive cough are often an immediate cause of death in patients with BO [62].

Diagnosis

Pulmonary function testing

Early and accurate diagnosis of BOS may enable the stabilization of pulmonary function at higher levels in transplant recipients [63]. However, the diagnosis of BO *per se* requires histologic confirmation. This may be difficult because of the suboptimal sensitivity of transbronchial biopsies (TBB) [7•]. Therefore, the ISHLT proposed a standardization of the nomenclature, and for clinical staging of chronic dysfunction in lung allografts [64,65]. As a result, BOS was proposed as a clinical description of BO and is defined by spirometric rather than histologic criteria. BOS is diagnosed when a patient has a decline of more than 20% in FEV1 compared with the mean of the two highest postoperative FEV1 values obtained 3 to 6 weeks apart. The decline in FEV1 should be present for at least 1 month, and should not be caused by other etiologies such as bronchial anastomotic stenoses, acute infection, or acute rejection [8]. Four stages of BOS are defined, which correspond to the degree of lung function impairment [64]. Estenne *et al.* [7•] published a proposal updating the diagnostic criteria for BOS, including the use of the forced expiratory flow rate between 25 to 75% of the forced vital capacity ($FEF_{25–75}$). Several authors have suggested that compared with the FEV1, the $FEF_{25–75}$ is more sensitive in detecting early airflow obstruction in BOS, despite the wider intrasubject variability of this latter index [66–68] (Table 2). Diffusing capacity (DLCO) is typically normal in the early stages.

Measurement of specific airway conductance may provide similar diagnostic information [69]. Response to bronchodilator therapy had a sensitivity of 51% and specificity of 81% in the prediction of subsequent BO in another study [70]. Use of ^{133}Xe-radiospirometry and dynamic spirometry in single lung transplant patients may show graft dysfunction at an earlier stage [71].

Hypoxemia and hypercapnia develop in end-stage disease only [72], and by this time decreased lung volumes [73] and decreased diffusing capacity [10] are present.

Lung biopsy

Lung biopsy is the only way to definitively diagnose BO, whether or not it is related to organ transplantation. Most lung transplant centers do not perform surveillance TBB after the first postoperative year, in part because of expense [8], and in part because of its invasive nature with risk of complications including hemorrhage and pneumothorax. Although TBB has a sensitivity of 80% and a specificity of nearly 100% in the diagnosis of acute rejection [74], its sensitivity in the diagnosis of BO varies between 15 to 82% [14,59,75,76]. This lower sensitivity is likely due to several factors, including the patchy nature of BO and the small quantity of bronchiolar material that is obtained, especially in the presence of airway fibrosis with scarring [76–78]. However, the sensitivity of this procedure increases with the increasing number of biopsies obtained (6 to 12), with higher yields at 10 to 12 biopsies. The number of procedures and the presence of an experienced bronchoscopist and lung pathologist also increase the sensitivity. [8,56]. In one study [77], TBB also provided histologic confirmation in 15% of patients diagnosed with BOS. Other authors [14, 79] have shown however, that TBB provided the diagnosis of BOS in up to 40% of patients. Nevertheless, a positive result from TBB has a high specificity and predictive value [56], approaching 94.5% for one set of transbronchial biopsies [76]. Surgical lung biopsy by video assisted thoracoscopic surgery (VATS), in the absence of a TBB diagnosis should be considered, especially if the case is atypical [10,56], as confirmation of another diagnosis may allow effective treatment.

Imaging

The CXR is normal in the early stages of BO, or may only show radiologic evidence of mild hyperinflation [56,63,80]. Further nonspecific abnormalities can be seen on the CXR as the disease progresses. These include areas of subsegmental atelectasis, volume loss, and/or fibrosis [10,60,63]. Changes consistent with bronchiectasis [81] may also be found. Parenchymal infil-

Table 2. Proposal to update the diagnostic criteria for bronchiolitis obliterans syndrome

Original classification		Current proposition	
BOS 0	FEV_1 80% or more of baseline	BOS 0	$FEV_1 > 90\%$ of baseline *and* $FEF_{25–75} > 75\%$ of baseline
		BOS 0-p	FEV_1 81% to 90% of baseline *and/or* $FEF_{25–75} \leq 75\%$ of baseline
BOS 1	FEV_1 66% to 80% of baseline	BOS 1	FEV_1 66% to 80% of baseline
BOS 2	FEV_1 51% to 65% of baseline	BOS 2	FEV_1 51% to 65% of baseline
BOS 3	FEV_1 50% or less of baseline	BOS 3	FEV_1 50% or less of baseline

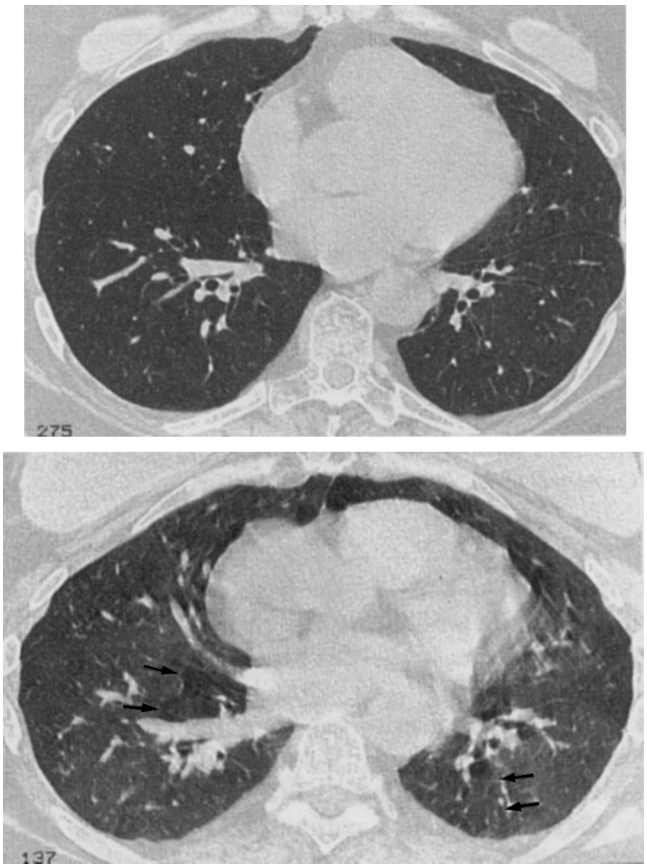
BOS, bronchiolitis obliterans syndrome; $FEF_{25–75}$, mid-expiratory flow rate; FEV_1, forced expiratory volume in 1 second.
Adapted from [7].

trates, on the other hand, tended not to occur unless pneumonia supervenes [56,81].

High resolution CT (HRCT) is a useful tool in the diagnosis of BO of any etiology. Early on, the most characteristic findings are segmental or lobular areas of hypoattenuation that are associated with narrowing of the caliber of the pulmonary vessels (mosaic perfusion) [82,83]. These abnormalities likely are consistent with air trapping, and can be clearly demonstrated on CT scans of the chest performed during expiration [84] (Fig. 2).

Mosaic perfusion has some sensitivity in the detection of BO occurring in lung transplant recipients [85] and likely represents diminished blood flow to hypoventilated areas due to reflex vasoconstriction [10]. However, Leung *et al.* [85] found that air trapping, as detected on HRCT, had a sensitivity of 91%, specificity of 80%, and accuracy of 86% for BO, and concluded that this radiologic indicator was the most sensitive and accurate for the detection of BO in the lung transplant population. On the other hand, Worthy *et al.* [86] found a sensitivity of 80% with a specificity of 94% for the diagnosis of BO using air trapping on expiratory HRCT as the radiologic indicator. Ikonen *et al.* [87] used a scoring system based on several HRCT findings to obtain a sensitivity of 93% with a specificity of 92% for the detection of BO.

Figure 2. Computed tomography scans of chest performed during expiration



Top: HRCT of a heart-lung transplant recipient with BO. Neither bronchiectasis nor a mosaic pattern of parenchymal attenuation is seen. Bottom: Corresponding HRCT at full expiration showing areas of hypoattenuation consistent with air trapping, especially in the lower lobes (see arrows). Adapted with permission [85].

Bronchiectasis is also a recognized and frequent association of BO, and tends to be peripheral and cylindrical in nature [60,88]. It is often a late finding, and therefore infrequently precedes the diagnosis of BOS [89]. Nevertheless, its presence suggests small airways obstruction [90].

Ventilation perfusion scanning in BO generally reveals diminished ventilation of the lung periphery. Although nonspecific, perfusion abnormalities may also be present, but these are usually much milder in nature than the ventilation abnormalities [56,91].

Prevalence and natural history

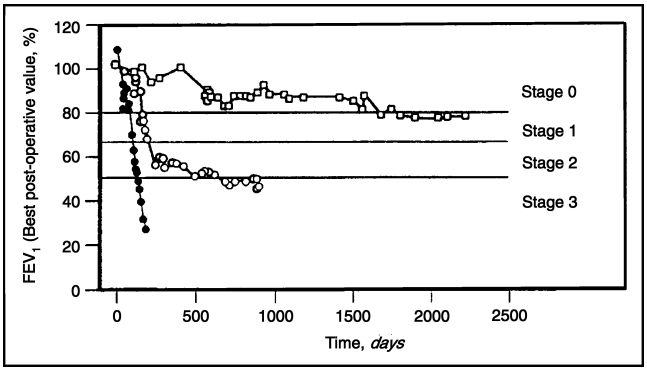
The overall prevalence for post-lung transplant BO (including BOS) varies from between 34 to 65%, with a 5-year probability of remaining free from the disease between 15 to 37% [8,14,15,79,92]. Several studies have also demonstrated that the prevalence of BO increases over time [14,93], and may reach 60 to 80% after 5 to 10 years post transplantation [94,95]. The incidence of non-transplant-related BO is rare. If present however, the most common association is with collagen vascular disease. In the opinion of the authors, the incidence of BO post-mycoplasma infection is below 5%.

The time between transplantation and onset of BO ranges from months to years, with a median time to diagnosis of between 16 to 20 months [8]. Its diagnosis is unusual prior to 3 months post transplantation.

However, once diagnosed, the natural history of BO is quite variable and unpredictable, with three distinct patterns reported in the literature [96,97] (Fig. 3).

The first pattern is one of rapid and relentless decline in FEV1 with ultimate respiratory failure and death within 1 year of diagnosis. The second pattern consists of an insidious onset, with slow progressive deterioration of the FEV1 with time. However, in a minority of patients with BO, a third pattern consisting of a rapid decline in FEV1 at the onset, followed by stabilization over a prolonged period of time, is seen. This third pattern accounted for only 20% of patients with BO/BOS 2 years after onset of the disease [15]. Furthermore, Kroshus *et al.* [19] showed that the risk for progression was higher in patients who developed BOS before the second postoperative year and also in patients with an increased number of acute rejection episodes that occurred within 6

Figure 3. Three distinct patterns of progression of bronchiolitis obliterans



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months of surgery. Conversely, Bando *et al.* [14] found that 87% of asymptomatic patients with BO (stage 0) resolved or stabilized their disease when diagnosed by surveillance TBB, suggesting that early diagnosis of BO with augmented immunosuppression initiated prior to the symptomatic phase may slow disease progression [8]. Some studies [15,61] also implicate a role for the number of lung infections and their method of treatment in the progression of BO.

Mortality

Patients with BO die mainly from infectious causes (60% of BO-related deaths) and ventilatory failure [10]. The overall mortality rate varies from between 25 to 56% with the risk increasing with time after diagnosis [14,93, 96,98]. Reichenspurner *et al.* [79] did not show a difference between heart-lung and single lung transplantation recipients, with a mean survival of 66, 37, and 10% at 1, 5, and 10 years, respectively [99].

Therapy

In general, medical treatment of BO is not fully satisfactory. Once established, BO is difficult to reverse, but augmented immunosuppression using various treatment regimens may achieve stabilization or at least slow the rate of decline in FEV1 for some period of time [8,56,63,92,100]. Ultimately, progressive deterioration usually ensues [101].

Augmentation of immunosuppressive therapy often begins with corticosteroids and/or cytolytic therapy in an effort to manage an active but potentially reversible inflammatory process [10,102,103]. The addition of azathioprine to cyclosporine and prednisone may stabilize pulmonary function in some patients [100].

"Anti-lymphocyte" antibody preparations can be used if high-dose intravenous methyl prednisolone pulses do not improve the FEV1 in a post-lung transplant patient with BO. In at least some of these patients, stabilization of the FEV1 occurs for 6 months or more [103, 104]. However, significant improvement in lung function is unusual [64]. This may, in part, be due to the fact that these anti-inflammatory therapies are not effective against the process of fibrosis that is occurring in the airways. In addition, these treatment strategies are delivered as "pulse therapy" because of the long-term side effects, especially infection and malignancy. Hence, relapses may be common [10,56].

Other immunosuppressive agents have also been studied. Kesten *et al.* [105] showed a significant reduction in the rate of decline of the FEV1 in patients with BO, when converted from cyclosporine to tacrolimus. Using a similar treatment conversion strategy, Ross *et al.* [106] showed spirometric stabilization over a 10-month follow-up period.

The substitution of mycophenolate mofetil for azathioprine [107,108] may also aid in the management of BO, but its effect possibly depends on the dosing regimen used [109]. In another study, the addition of methotrexate to the immunosuppressive regimen was shown to stabilize lung function in patients with BO unresponsive to steroids or anti-lymphocyte preparations [110]. However, concerns for pulmonary and hepatic toxicity as a side effect of methotrexate remain.

Unfortunately, the effectiveness of many of these studies can be difficult to define because of the relatively small number of patients studied and relatively short follow-up periods [8]. In addition, it is unclear as to whether these treatment strategies are definitely effective in changing the natural history of BO [111].

Nevertheless, other reported treatment strategies include the use of inhaled cyclosporine in an effort to achieve a higher targeted drug level in the lung with fewer systemic side effects [10]. Iacono *et al.* [112] reported on seven of nine patients with BO who had stabilization of pulmonary function and histologic improvement after inhaled cyclosporine A. Cough was a major side effect. It is possible that the beneficial effect of cyclosporine was due to detectable blood levels of this drug after aerosolization rather than due to its local effects in the lung [10,56].

Inhaled high-dose corticosteroids (fluticasone propionate) may also have a beneficial effect in BO. Speich *et al.* [113] reported on a double blind, randomized trial of inhaled fluticasone propionate in a patient with post-transplant BO, and showed an increase in the FEV1 while on fluticasone.

Other treatment strategies

Extracorporeal photochemotherapy [114] and total lymphoid irradiation [115] have also been used as immunomodulating treatment for BO. Novel agents, such as

rapamycin and leflunomide, which act on the late fibroproliferative response in BO [10] may also be found to be beneficial in the management of BO [79,116].

Retransplantation, the most aggressive treatment for advanced BO, is the treatment of last resort [8,92], and can be somewhat controversial [117•]. Brugiere *et al.* [118•] suggest that replacement of the primary graft during retransplantation may avoid potentially fatal infectious complications that can occur if the old graft is left *in situ*. In carefully selected patients who are ambulatory and not ventilator dependent, the medium-term prognosis for retransplanted patients is similar to that for first-time lung transplant recipients [119]. Once retransplanted, such patients do not appear to develop BO in an accelerated manner. Their risk of developing BO is similar to that of first-time lung transplant recipients, in the region of 38% at 2 years [119].

Conclusion

Bronchiolitis obliterans remains a major cause of lung allograft dysfunction and has a variable course. It is the major hurdle to long-term survival in lung transplant recipients, and once established various treatment strategies including augmented immunosuppression have been disappointing in terms of efficacy and ability to recover lost lung function. Under these circumstances, and while awaiting more effective treatment methods, minimization of risk factors for BO, especially acute rejection episodes, preemptive therapy for CMV, and early detection of BO in the asymptomatic stage likely allow the best chance for stabilization and/or resolution of this unfortunate disease.

These concluding statements refer mainly to posttransplant BO. However, based on our limited understanding of the pathophysiology of nontransplant BO, and from our own clinical experience, and anecdotal reports, the progression of nontransplant BO appears less aggressive than that of posttransplant BO. Nevertheless, the response to steroid therapy in terms of recovery of lost lung function remains poor in both cases. Early detection of nontransplant BO utilizing various methods including methacholine challenge testing and expiratory HRCT scans of the chest will hopefully allow earlier identification of this disease entity and minimize loss of lung function that is often irrecoverable.

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- •• Of outstanding interest

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