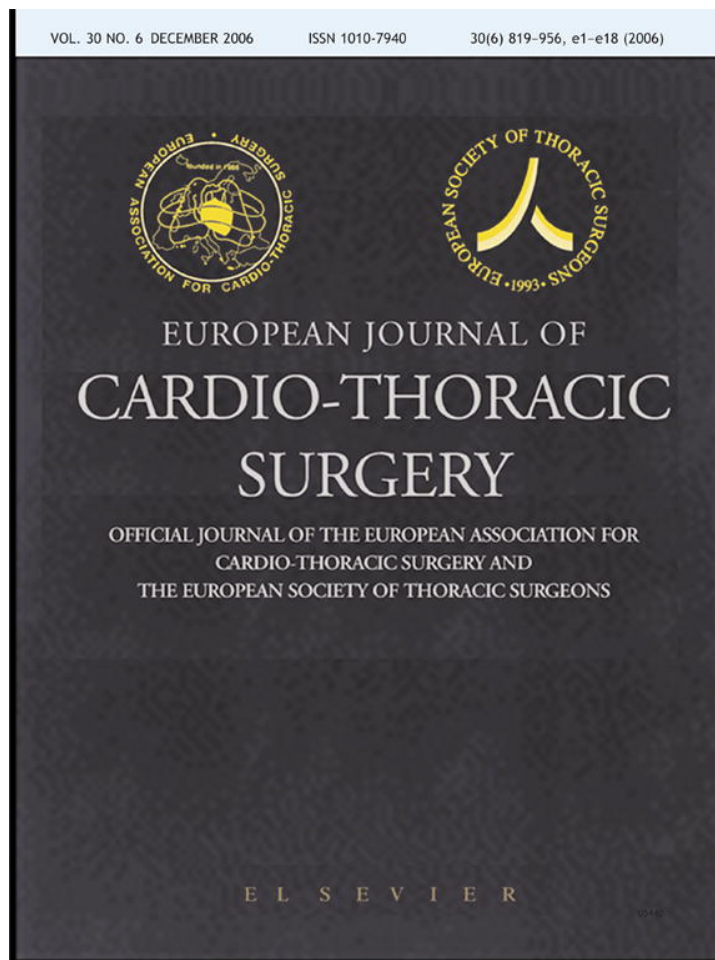


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Review

## Bronchiolitis obliterans following lung transplantation

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### Summary

Bronchiolitis obliterans syndrome (BOS) is the main and late chronic complication after lung transplantation. It remains a major impediment to long-term outcome. Unfortunately, the survival rate of lung transplant recipients lags behind that of other organ transplant recipients, and BOS accounts for more than 30% of all mortality after the third year following lung transplantation. Most recent studies suggest that immune injury is the main pathogenic event in small airway obliteration and the development of BOS. Early detection of BOS is possible as well as essential because prompt initiation of treatment may halt the progress of the disease and the development of chronic graft failure. Current treatment of BOS is disappointing despite advances in surgical techniques and improvements in immunosuppressive therapies. Therefore, a clear understanding of the pathogenesis of BOS plays a major role in the search for new and effective therapeutic strategies for better long-term survival and quality of life after lung transplantation.

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**Keywords:** Lung transplantation; Bronchiolitis obliterans; Pathogenesis

### 1. Introduction

Bronchiolitis obliterans syndrome (BOS) following lung transplantation was first described at Stanford University in heart–lung transplant recipients who developed a progressive deterioration in forced expiratory volume in 1 s (FEV1) [1]. Their transbronchial lung biopsy revealed intraluminal eosinophilic granulation tissue and extensive submucosal eosinophilic infiltrates.

BOS, which is defined as a progressive airflow obstruction and a deterioration of graft function, is a major complication following lung transplantation [2]. It affects up to 60% of recipients who survive 5 years after surgery [3].

The median time to diagnose BOS is 16–20 months following transplantation. In most patients, BOS is a progressive process that responds very poorly to immunosuppressive therapies. It accounts for more than 30% of all mortality after the third year following lung transplantation [4]. Survival at 5 years after the onset of BOS is 30–40% and survival at 5 years after transplantation is 20–40% lower in patients with BOS than in patients without it [5]. In addition,

early onset of BOS has a more deleterious effect on functional parameters (mean FEV1, 6 min walk test, O<sub>2</sub> dependency) than does late onset [6]. Owing to the difficulties in conducting an adequate transbronchial biopsy, due to the patchy distribution of the disease, BOS is also defined as irreversible decline in FEV1 of at least 20% of the predicted baseline value, and, according to the 1993 staging system of the International Society of Heart and Lung Transplantation (ISHLT), it is graded as BOS stage 1, FEV1 between 66 and 80% of the baseline; BOS stage 2, FEV1 between 51 and 65% of the baseline; and BOS stage 3, FEV1 between 0 and 50% of the baseline. This staging system has been adopted by all transplant centres worldwide. But new staging criteria have been formulated for the early detection of allograft dysfunction, which include the 'Potential BOS' stage (BOS<sub>0-p</sub>), defined as a 10–19% decrease in FEV1 or a 25% or more decrease in forced mid-expiratory flow rate (FEF<sub>25–75%</sub>) from the baseline [7,8]. The rationale for including FEF<sub>25–75%</sub> stems from numerous studies have suggested this variable decline before FEV1 at the onset of BOS [9–11].

### 2. Pathogenesis

A better understanding of BOS pathogenesis is important if rational strategies are to be developed for its management. The histological pictures of BOS suggest that repeated injury

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and inflammation of the epithelial and subepithelial cells coinciding with defective regeneration lead to excessive fibroproliferation and obliteration of small airways. Two hypotheses have been proposed to explain the pathogenesis of chronic rejection.

### 3. Antigen-dependent factor

Influenced by research into early immunological injury, several studies have demonstrated that acute rejection is one of the most important risk factors for the development of BOS [12,13]. However, many patients with a history of acute rejection do not develop BOS, while some patients with BOS have never had acute rejection. In addition, several studies have identified that airway epithelial cells are immunological targets [14] that are able to express MHC class I and II molecules—both are up-regulated in rejecting lung epithelia but not in normal lung epithelia [15–17]. One study demonstrated that lung transplant recipients with BOS developed *de novo* airway epithelial cell antibodies that diverted towards donor-specific class I MHC antigens [18]. In addition, these antibodies did not react to different panel cell lines such as smooth muscle cells and fibroblasts. The presence of anti-MHC class I and class II that developed before the onset of BOS development is a predisposing factor of BOS [19]. However, these lines of studies do not provide evidence that HLA mismatching is a risk factor for BOS.

### 4. Alloantigen-independent factors

The lung is a vulnerable organ because it is consistently exposed to exterior agents, such as inhaled dust, toxins, infectious materials and irritants, which promote local inflammation and trigger the development of BOS.

Bacteria and fungal infections may increase the risks of acute rejection and chronic allograft dysfunction. In contrast, CMV-related illnesses have been implicated in chronic vascular rejection of other solid organ transplants [20]. Many transplant centres have reported that CMV pneumonitis is a significant risk factor for BOS [21,22]. It is believed that CMV infection promotes allograft rejection through the production of cytokines and the increased expression of MHC. Ganciclovir prophylaxis creates a significant delay in the development of BOS [23].

Other non-CMV viral infections may trigger the development of BOS. This is based on a study that showed that the onset of BOS was seasonal and correlated with the peak season for different respiratory viruses such as influenza and parainfluenza, respiratory syncytial virus and adenovirus [24].

The role of airway ischemia as a risk factor for the development of BOS is not clear, though Bando et al. [13] have demonstrated that airway ischemia within the first 14 days following transplant had an effect on BOS. Some groups suggest that restoring bronchial arterial circulation by reanastomosis of the bronchial artery with the recipient internal mammary artery [25] may postpone the onset of BOS [26].

The impact of donor age and ischemic time as suspected risk factors for BOS remain unconvincing. Sommers et al. [27] found that older donor age correlated with early graft dysfunction within the first hours after lung transplantation. New data, however, indicates that donor age did not appear statistically significant affect on the incidence of BOS and survival at 1 year post-transplantation [28]. Similarly, prolonged ischemic time did not independently increase risk of BOS. Only combination of older donor (age > 55 years) and prolonged ischemic time (>7 h) demonstrated negative influence on survival at 2 years post-transplantation [29].

Recently, gastric aspiration has been reported as a risk factor for BOS. Gastroesophageal reflux disease is common after lung transplantation due to intraoperative vagal nerve injury. In addition to medication-induced gastroparesis and airway denervation, transplant patients are at risk of aspiration that may induce chronic inflammation and bacterial infection [30].

The concept of 'response to injury' suggests that injury induces a stereotyped injury response that promotes immune recognition. This response injury becomes self-propagating to the extent that it becomes irreversible.

### 5. Early detection

Early identification and preclinical detection of BOS are important goals. According to the ISHLT, the diagnosis of BOS after transplantation is based on histological and spirometric staging criteria. Because BOS is progressive and irreversibly affects the distal airways with a patchy distribution, detection of it early on is difficult. However, several parameters have been studied to identify their potential usefulness as markers for early detection of BOS.

### 6. Pulmonary function tests

Pulmonary function tests are routinely performed after transplantation as persistent decline in FEV1 of 20% or more of the baseline value in the absence of infection and acute rejection is a useful clinical surrogate. The Stanford University group demonstrated a decline in the forced expiratory flow (FEF<sub>25–75%</sub>) to less than 70% of the predicted values occurring 4 months earlier than the 20% decline in FEV1 [11]. This appears to be a sensitive marker for the early detection of BOS. The methacholine challenging test at 3 months post-transplantation has predicted the early detection of BOS with a positive predictive value of 72% [31].

### 7. Transbronchial biopsy

Surveillance transbronchial biopsies are very useful in the diagnosis of acute rejection, with variable sensitivity in the range of 22–73% of clinically and physiologically stable patients [32]. Furthermore, transbronchial biopsies do not get enough sensitivity in BOS due to the patchy distribution of the disease [33]. The Stanford experience found the total

sensitivity of a transbronchial biopsy to be 30.7% for each biopsy specimen, and they have recommended that at least 8–10 tissue specimens be taken from different pulmonary lobes. Since then, the sensitivity of transbronchial biopsies has increased to 71.4% in 42.8% of all cases [34].

### 8. Bronchoalveolar lavage

Bronchoalveolar lavage (BAL) provides a unique method of assessing the cellular components of the lower respiratory tract, and BAL cellularity may be a signal for post lung transplant complications. Evidence of an increase in neutrophils in stable lung recipients in BAL fluid is a probable indication of subclinical alloimmune stimulation and the development of BOS [35,36]. Currently, the contribution of neutrophils in BAL to the pathogenesis of BOS is still debatable. Di Giovine et al. and Reynaud-Gaubert et al. have pointed out that airway neutrophilia constitutes an early marker of BOS [37,11].

### 9. Computed tomography

Air trapping on an expiratory CT scan is not necessarily indicative of disease and may be seen in healthy individuals [38,39]. But at a threshold of 32% (determined by receiver operative characteristic analysis and approximates one-third of lung parenchyma) found to have 80–90% sensitivity, 80–94% specificity and 86% accuracy in the detection of BOS [40].

### 10. Exhaled nitric oxide fraction

Nitric oxide (NO) has been implicated in the pathophysiology of airway diseases [41]. The fraction of NO in exhaled breath correlates with the level of NO formed in airway epithelia. The level increased with airway inflammation [42] is found to be very high in patients with BOS [43–45]. This test may be very useful in the early detection of BOS after lung transplantation.

### 11. Treatment options

The treatment of established BOS is deceptive and it is usually unresponsive to medical therapies. Modern modalities of treatment include augmenting immunosuppression, modification of immunosuppression agents and immune modulation.

### 12. Augmenting immunosuppression

Augmentation of immunosuppression agents in the early stages of BOS may arrest the progression of the disease by increasing the dose of methylprednisolone with azathioprine or ATG and OKT3 [46]. Unfortunately, this is an anecdotal approach and has disappointing outcomes, though it is still given at most transplant centres.

### 13. Modification of immunosuppression therapy

The change of calcineurin inhibitors from cyclosporine A to tacrolimus has proved to be effective in the treatment of new-onset BOS [47]. Keenan et al. randomised 133 recipients to receive either cyclosporine A or tacrolimus in addition to azathioprine and a steroid. Reduced incidences of BOS (38% vs 22%) were observed in the tacrolimus group [48,49], but there was no significant difference in survival after 2 years.

### 14. Immune modulation therapies

Extracorporeal photopheresis (ECP) was first used to treat cutaneous T-cell lymphoma. Its mechanism of action in the modulation of T-cells is not clear, but a few reports suggest that ECP acts as follows: first, it induces a release of non-specific inflammatory mediators (interleukin (IL)-1, interleukin-6 and tumour necrosis factor alpha); second, it induces a apoptosis of peripheral blood T-cell populations; third, it induces a clone-specific suppressor T-cell response [50,51]; and fourth, it induces 'photodestruction' long-wavelength ultraviolet-A light, which activates 8-methoxypsoralen, leading to the cross-linking of DNA and resulting in the inhibition of cellular proliferation [50]. Very few reports have described the effect of ECP in lung transplant recipients with BOS [52]. Slovis et al. [53] reported that 3 out of 3 recipients with severe BOS showed improvement and stabilization in pulmonary function.

### 15. Total lymphoid irradiation

Radiation delivered twice weekly in 0.8 Gy fraction with a total dose of 8.0 Gy to the major lymphatic areas, which include three fields. The mantle field includes the low cervical, supraclavicular, infraclavicular, axillary, mandibular and hilar lymph nodes, and the thymus gland. The paraaortic field includes the paraaortic lymph nodes and the spleen. The inverted-Y field includes the iliac, inguinal and femoral lymph nodes. Diamond et al. gave the standard medical treatment to 11 recipients with advanced BOS refractory. Four of the 11 recipients showed a favourable response to total lymphoid irradiation, suggesting that a positive response to total lymphoid irradiation requires a longer interval between transplant and radiation, higher FEV1 at the initiation of radiation and an absence of pre-existing pulmonary infection [54].

### 16. New therapeutic and prevention strategies

*Macrolides*, such as azithromycin and clarithromycin, both of which are non-bacteriocidal macrolides, produce an effect through the inhibition of certain pathogens such as *Pseudomonas aeruginosa*. Azithromycin may exert an anti-inflammatory effect and inhibit the immune response. This was shown by a significant reduction of airway neutrophilia after 3 months of treatment [55]. In a double-blind study, clarithromycin significantly reduced interleukin-8 level in patients with COPD [56]. It is well

known that IL-8 is chemo-attractive for neutrophils elevated in BAL fluid in patients with BOS [37]. Gerhardt et al. [57] demonstrated a statistically significant improvement in pulmonary function in five out of six recipients with BOS who were treated with oral azithromycin.

### 16.1. Statins

3-Hydroxymethyl-3-methylglutaryl coenzyme A reductase inhibitors are blood cholesterol lowering agents that are known to have immunomodulatory actions independent of the blood cholesterol level [58]. Many reports have described how statins reduce lung ischemic reperfusion injury [59]. Also, they inhibit the up-regulation of MHC class II expression, which is an important component of allograft rejection. In a retrospective study, Johnson et al. analysed data on 39 lung transplant recipients who were receiving statins for hyperlipidemia and 161 control recipients who did not receive statins. Among the recipients treated with statins, there was a significant reduction in parameters (few episodes of acute allograft rejection and few neutrophil cells on BAL). None of the recipients on statins developed BOS during the first post-operative year. The authors concluded that statins may improve the outcome after lung transplantation [60].

*IL-2 receptor antagonists* (daclizumab, basiliximab) are humanised or chimeric monoclonal antibodies directed against IL-2 receptors that selectively block activated T-cells. In a 4 years prospective, non-randomised study, 87 lung transplant recipients were divided into three treatment arms. Arm 1 received OKT3, arm 2 received ATG and arm 3 received daclizumab. No differences in the incidences of acute rejection and patient survival were found. The incidences of BOS and infection were lower in the daclizumab arm, though the follow up for this treatment arm was shorter [61].

### 16.2. Early fundoplication

Gastroesophageal reflux disease (GERD) is common in patients with end-stage pulmonary disease, particularly those with idiopathic pulmonary fibrosis and cystic fibrosis [62]. In a retrospective study, Cantu III et al. [63] demonstrated non-conclusively, a survival advantage in the early fundoplication in lung transplant recipients with GERD, and suggested that early fundoplication may retard the development of BOS and as a consequence extend survival.

### 16.3. Lung retransplantation

The issue of lung retransplantation is a complex and raises several points; long-term outcome, recurrence of BOS and ethical principles. Most lung transplantation centres will consider retransplantation on individual case-by-case basis.

The outcome of lung retransplantation remains generally unfavourable, with 1 and 3 years survival of 47 and 33%, respectively [64]. New data, from recent studies demonstrated long-term outcome after retransplantation, survival at 1 and 5 years were 78 and 62% [65], which are not significantly different from those reported after primary lung transplantation. Brugiere et al. [66] data of 15 lung recipients

with severe BOS underwent single lung transplantation showed, survival at 1, 2 and 5 years was 60, 53 and 45%, respectively. These wide variations in results would reflect differences in patient selection for retransplantation.

The recurrence of BOS is not greater for retransplant patients and lung retransplantation should be considered as a viable option for patients with severe BOS [67].

Another consideration is ethical principles, which required full understanding and investigation as part of the lung retransplantation process.

## 17. Conclusion

Lung transplantation is a challenging but important field for future basic and clinical scientific research. Despite advances in surgical techniques and in immunosuppressive therapies, the prevention and treatment of bronchiolitis obliterans syndrome remain disappointing. We believe that a clear understanding of the pathogenesis of BOS will facilitate the discovery of new and effective therapeutic strategies to halt the progress of this disease, resulting in a substantial improvement in long-term survival after lung transplantation. Lung retransplantation for BOS is the only definitive therapeutic option and shall be considered in selected group of patients. As lung transplant clinicians, we strive to improve the quality of patients lives and exert every effort to simplify the complexity of their lives as a result of disease progression.

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