Bronchiolitis obliterans syndrome

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Abstract Bronchiolitis obliterans syndrome (BOS) is thought to represent chronic allograft rejection. Primary graft dysfunction (PGD), acute cellular rejection (AR), lymphocytic bronchiolitis (LB), abnormal gastroesophageal reflux (GER) with microaspiration, and allograft infection have all been implicated as causes of BOS. Although BOS is generally considered to be caused by alloimmune responses to non-self tissue, more recent findings suggest that autoimmune responses to self-antigens and the triggering of innate immune responses to environment stimuli may play a significant role in the pathobiology of BOS. Effective treatment of BOS remains elusive, but azithromycin may stabilize and possibly improve FEV1 in patients who meet criteria for BOS, and gastric fundoplication may be beneficial if abnormal GER is detected. Augmented immunosuppression is generally ineffective, and other treatments such as total lymphoid irradiation (TLI) or extracorporeal photopheresis (ECP) may not have a significant impact on loss of function. Retransplantation can be considered in carefully selected patients.

Keywords Lung transplant · Bronchiolitis obliterans syndrome · Obliterative bronchiolitis · Chronic lung allograft dysfunction

Introduction

Bronchiolitis obliterans syndrome (BOS) represents the greatest threat to long-term survival following an initially

successful lung transplant (LTX). Loss of allograft function that meets criteria for the diagnosis of BOS (see Table 1 for current diagnostic criteria and staging) is attributed to the onset of a constrictive bronchiolitis that leads to airway fibrosis and disappearance of small airways due to luminal obliteration and cicatrix formation that has been termed obliterative bronchiolitis (OB) [1–4].

OB was first described in lung allograft tissues from heart-lung transplant recipients in 1984 [5] and was associated with delayed onset of declining allograft function and airflow obstruction following initial recovery from transplant and stabilization of graft function. OB was subsequently found to be a common histopathologic finding when delayed allograft dysfunction associated with a pattern of airflow obstruction on spirometric testing occurred in lung or heart-lung transplant recipients [6, 7]. However, definitive histopathologic changes are frequently absent when tissue sampling is relatively limited (despite the presence of OB), due to the small size of the forceps biopsy specimens obtained via transbronchial lung biopsy (TBB), the patchy nature of the lesions, and bronchoscopist-dependent sampling adequacy [8, 9]. Because of the association of OB with an obstructive pattern of lung function decline and the difficulty of obtaining adequate lung tissue via TBB to make a confident diagnosis of OB, FEV1 was chosen as a surrogate marker that could be used to indicate the likely presence of OB if other, potentially reversible causes of allograft functional decline are excluded as a cause of FEV1 decline [6].

Although a number of advances have been made in surgical techniques and early management that have improved early LTX outcomes, this has had little impact on the prevalence and outcome of BOS in LTX recipients. More than 50 % of lung allograft recipients will develop clinically significant BOS [4], which is a common cause of graft loss and patient death. Strategies to prevent BOS as

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Table 1 Criteria for diagnosis and staging of BOS

BOS grade	Spirometry (% of baseline)
0	FEV ₁ >90 % of baseline and FEF ₂₅₋₇₅ >75 % of baseline
0-p	FEV ₁ 81–90 % of baseline and/or FEF ₂₅₋₇₅ ≤75 % of baseline
1	FEV ₁ 66–80 % of baseline
2	FEV ₁ 51–65 % of baseline
3	FEV ₁ ≤50 % of baseline

Baseline defined as the average of the two best FEV1 determinations post-LTX obtained at least 3 weeks apart (J Heart Lung Transplant 2002;21:297–310)

well as strategies to detect it in early stages and effectively arrest it and prevent its progression and loss of allograft function are much needed to improve long-term survival following LTX.

Terminology of lung allograft dysfunction

The revised BOS classification system published in 2002 [10] states that lung function decline should be determined by comparing values obtained over time to an optimal, post-transplant baseline value (Table 1). The baseline value for FEV1 and FEF25–75 is the average of two highest values for each measurement obtained at least 3 weeks apart post-transplant (without the administration of a bronchodilator). By definition, 3 or more months are required to have elapsed from the date of the transplant for the diagnosis of BOS to be made to help distinguish BOS from acute and/or subacute complications of lung transplantation as well as taking into account the time needed to establish both a baseline FEV1 and the 3-week interval needed to confirm a significant decline in FEV1 (via a second measurement) that meets the criteria for a diagnosis of BOS [6, 10]. In practice, it may be difficult to establish a baseline with two reasonably concordant measurements 3 weeks apart due to various complications (e.g. acute rejection or infection) that may cause considerable undulation of FEV1 values over time, making it difficult to establish a stable baseline for some recipients. Due to concern that setting the cutoff value for FEV1 at 80 % of the best post-transplant value may be insensitive to early decline in allograft function due to early OB, the revised statement created stage BOS-0p (≥10 % decline in FEV1 and/or ≥25 % decline in FEF25–75) to signify “potential BOS” [10].

As our understanding of delayed lung allograft dysfunction has evolved over the past decade, it has become clear that many factors (e.g. acute rejection, infection, pleural disorders, anastomotic dysfunction, impaired allograft inflation, inflammatory disorders, recurrent parenchymal disease) may cause graft dysfunction beyond the acute post-transplant time period, and

declining graft function that meets criteria for BOS may not necessarily be due to the development of clinically significant OB. The terms chronic lung allograft dysfunction (CLAD) and chronic rejection have increasingly appeared in the literature and are frequently used synonymously or interchangeably with OB and BOS [11•, 12•, 13•]. However, CLAD needs to be more rigorously defined and may be observed when entities other than OB/BOS are present or when a combination of factors (which may include OB as one of the pathologic entities) negatively impact allograft function. Additionally, lung function decline consistent with a diagnosis of BOS can stabilize in some patients and not lead to sustained, progressive deterioration in allograft function and graft loss, as discussed below. Finally, the entity of restrictive allograft syndrome (RAS) has been recently described as a form of delayed allograft dysfunction characterized by parenchymal fibrosis that can be distinguished from typical BOS/OB [11•, 13•, 14••]; OB lesions may be present in lung specimens from recipients who develop this type of lesion, but restrictive physiology and radiographic parenchymal infiltrates are typically present (in contrast to OB/BOS, which is characterized by obstructive physiology and lacks significant parenchymal fibrosis).

Phenotypes of BOS

The identification of characteristics that identify subsets of BOS patients (differing disease mechanisms, risk factors, and responses to treatment interventions) may aid efforts to provide specific treatments and make key management decisions. Recipients with early onset BOS may represent a group that is prone to rapid progression and poor prognosis [15–18], although, some patients with rapidly declining lung function may stabilize despite an initial rapid onset and FEV1 decline [19]. Recent investigations have also described a phenotype of significant bronchoalveolar lavage (BAL) neutrophilia that is often associated with high-resolution computed tomographic (HRCT) changes of probable cellular bronchiolitis, and these individuals usually respond to azithromycin therapy [20•, 21•]. Indeed, FEV1 may improve such that the recipient no longer meets spirometric criteria for BOS, and this entity has been labeled neutrophilic reversible allograft dysfunction (NRAD) [1, 20•]. It has also been suggested that patients who meet BOS criteria but do not respond to azithromycin may represent a fibroproliferative OB phenotype [20•]. However, distinct phenotypes of BOS that are based upon specific risk factors or other parameters have yet to be definitively established.

Pathogenesis and mechanisms of obliterative bronchiolitis

Lung histopathology in patients with BOS shows striking similarities to the OB that can occur in allogeneic bone

marrow or stem cell transplant recipients as well as constrictive bronchiolitis in patients with connective tissue diseases, and these airway changes are perceived as alloimmune or autoimmune disorders respectively. BOS is widely perceived as the physiological surrogate (FEV1 decline) of the effects of an alloimmune response to foreign tissue due to many observations that include its association with acute cellular rejection [22] and greater degrees of HLA mismatch [23]. Indeed, early acute allograft rejection and late/refractory acute rejection and late lymphocytic bronchiolitis (LB) are prime risk factors (Table 2) for developing BOS [24–31]. Additionally, humoral rejection (e.g. de novo anti-HLA antibodies) has also been associated with the development of BOS [32, 33]. Nonetheless, although BOS is frequently equated with the term chronic rejection, various interventions including intensified immunosuppression may have little or no effect on the progressive loss of allograft function that is usually observed in transplant recipients who develop BOS.

More recent investigations have linked autoimmune sensitization to self-antigens (collagen V or K-alpha-1-tubulin) to BOS [34, 35•], and alloimmune responses may stimulate or drive such autoimmune responses, which may involve Th17 cells and IL-17 [35•]. In addition to alloimmune and/or autoimmune phenomena associated with BOS, many mechanisms that can be perceived as predominantly non-immune have been implicated as playing a role in BOS pathogenesis. These include injury caused by primary graft dysfunction (PGD) [36, 37], gastroesophageal reflux (GER)

with microaspiration [38, 39], airway ischemia caused by disruption of the bronchial circulation [40•], and infections caused by viruses [41, 42], bacteria [43, 44], or fungi [45]. These “non-immune” factors may promote tissue inflammation that in turn initiates and may intensify an alloimmune rejection response or autoimmune reaction to lung airway self-antigens. Finally, it has been suggested that environmental exposures may lead to airway injury and obliteration, and higher ambient levels of pollutants have been linked to BOS in lung transplant recipients [46]. Indeed, these “non-immune” stimuli may induce BOS by triggering innate immune responses [3], which may then also interact with cellular and humoral arms of adaptive immunity that determine alloimmune and autoimmune responses against non-self (e.g. MHC mismatched allograft antigens) as well as allograft self-antigens (e.g. collagen V).

OB/BOS pathogenesis is thought to involve a primary stimulus that activates resident airway dendritic cells and/or airway macrophages, which leads to up-regulation of chemokines and cytokines of epithelial and endothelial origin. This local inflammation attracts and activates additional inflammatory cells, especially lymphocytes and neutrophils, and also provokes the production of cytokines by structural airway cells such as myofibroblasts and smooth muscle cells. Interleukin-17-producing cells (Th17 cells) have been linked to the constrictive bronchiolitis of BOS and may be the prime stimulus for upregulation of IL-8, which is a potent chemoattractant of neutrophils [47, 48]. As airway inflammation progresses, epithelial and interstitial damage is likely induced by reactive oxygen intermediate production and matrix metalloproteinase (MMP) production [49, 50]. Epithelial-mesenchymal transition can occur in response to epithelial damage and lead to the fibroproliferative changes that cause airway scarring and obliteration [51, 52•], and allograft fibroproliferative responses may be driven by resident mesenchymal cells [53]. Additionally, accelerated senescence of epithelial or other allograft cell types may play a role in predisposing the allograft to developing chronic airway dysfunction and BOS [54].

Because established OB displays variable evidence of inflammation, alloimmune reactions, autoimmunity, and fibroproliferation with airway obliteration that leads to allograft airway remodeling and loss of function, OB may well represent a final common end-point for allograft bronchiolar injury precipitated and/or driven by a variety of insults and mechanisms. Indeed, innate immune responses to a variety of environmental insults (LPS from airway bacteria, refluxed non-acid gastric contents that contain LPS due to gram-negative bacterial overgrowth, viral infection, fungal colonization, or air pollution) via toll-like receptor (TLR)-mediated pathways may play an important role in the induction and progression of BOS, and some LTX recipients may have genetic polymorphisms (e.g. TLR4, CD14) that make

Table 2 Risk factors associated with the development of BOS

• Primary graft dysfunction
• Acute cellular rejection
• Lymphocytic bronchiolitis
• Humoral rejection (e.g. anti-HLA antibodies)
• Gastroesophageal reflux and (micro)aspiration
○ Acid reflux
○ Non-acid reflux
• Infection
○ Cytomegalovirus
○ Community-acquired virus infection
○ Bacterial colonization/infection (e.g. <i>Pseudomonas</i>)
○ Fungal colonization/infection (e.g. <i>Aspergillus</i>)
• Autoimmune sensitization to self-antigens
○ Collagen V
○ α -k-tubulin
• Air pollution
• Inadequate recipient compliance with outpatient drug therapies
• Other potential risks
○ Accelerated allograft aging due to cellular senescence
○ Ischemic airway injury due to disrupted bronchial microcirculation

them more susceptible to triggering of innate immune responses [3]. As mentioned above, although BOS is frequently equated with the term chronic rejection, intensified immunosuppression may have little or no effect on the progressive FEV1 decline that is commonly observed unless a response occurs to treatments such as azithromycin.

Bronchoalveolar lavage neutrophils and BOS

Persistent increases in BAL neutrophils have been observed in patients with allograft complications such as infection, acute rejection, LB, and established BOS [55, 56], and BAL neutrophilia has been linked to BOS [57–59] and identified as a predictor of increased overall mortality risk [60]. As mentioned above, Vos et al. [20•] have shown that recipients who meet criteria for BOS but have significantly increased numbers of neutrophils in BAL (generally greater than 15 % on differential cell count) are likely to respond to azithromycin therapy and may regain function such that BOS criteria are no longer met. HRCT scans in these patients tend to show changes consistent with cellular bronchiolitis that clear with effective azithromycin therapy.

Diagnosis of BOS

Once patients stabilize following transplantation, their clinic visits gradually decrease in frequency if they have recovered well and are clinically stable. However, patients need to be educated to recognize and promptly report symptoms that may indicate that respiratory or other complications are developing. Follow-up clinic visits typically include spirometry and routine chest radiographs, and a 6-MWT may also be performed. Some studies suggest that a decline in FEV1 that meets the FEV1 criterion for BOS Stage 0p (a 10–19 % decline in FEV1 from baseline) correlates with an increased risk of evolving OB/BOS [61–63]. The lower sensitivity and specificity of the FEF_{25–75} criterion for BOS Stage 0p (≥ 25 % decline), however, appears to make a decline in this measurement less reliable for predicting the early onset of evolving OB/BOS. In addition to routine imaging and pulmonary function testing, surveillance bronchoscopies are performed by a majority of transplant centers in the US [64], especially during the first year after transplant, and BAL and transbronchial biopsies performed when surveillance bronchoscopy is performed can frequently detect occult infection or rejection [65]. There is general consensus that prompt and effective treatment of these entities (even when patients are clinically stable) may decrease the risk of developing BOS.

Many centers have patients perform once or twice daily home spirometry to track FEV1 following successful lung

transplant and subsequent stabilization of graft function, and a decline in FEV1 needs to be reported to the transplant center so that a prompt evaluation can be undertaken. Concern for possible BOS should trigger an evaluation to determine the cause of lung function decline. In addition to a clinical evaluation with history and physical examination, a routine chest radiograph and spirometry are typically obtained. Additionally, the 6-MWT test can be useful to detect a significant decline in walk distance and/or significant oxyhemoglobin desaturation that was not present on previous clinic evaluations. Bronchoscopy is typically performed with BAL and transbronchial biopsy to rule out acute rejection or infection as a cause, and biopsy specimens may occasionally be obtained that are diagnostic of OB. HRCT imaging may be useful to detect abnormalities for which the routine chest radiograph is insensitive, and HRCT imaging with expiratory imaging may reveal changes of cellular bronchiolitis, bronchiectasis and/or air trapping consistent with bronchiolitis [66–68]. A thorough evaluation can detect rejection, infection, or other causes of delayed lung function decline that meets the definition of BOS. It should be kept in mind that more than one pathologic process may simultaneously affect the lung allograft, and detection of initial stages of allograft dysfunction due to evolving BOS may be somewhat difficult in patients who receive single LTX for pulmonary fibrosis. Although many potentially useful biomarkers have been examined and reported, a biomarker that possesses good sensitivity and specificity to predict the presence of BOS versus other causes of declining lung function has yet to be found.

Management of BOS

Considerations for the management of BOS are given in Table 3. Because BOS has been perceived as representing a form of allograft rejection and the administration of high-dose corticosteroids is a standard treatment measure for newly detected AR that can usually reverse an acute decline in lung function and stabilize the patient, intensified immunosuppression has been viewed as a logical strategy for treating BOS. However, there are no data to support intensified doses of corticosteroids as an effective therapy for BOS, and one study reported a lack of response to repetitive administration of pulsed, high-dose methylprednisolone [69]. Additionally, chronic or pulse high-dose corticosteroid administration is associated with numerous, significant adverse side effects and is not likely to stabilize or improve the course of BOS. Other treatments such as the administration of cytolytic agents, the addition of cytotoxic drugs such as cyclophosphamide or methotrexate, the use of aerosolized cyclosporine A, or the addition of an mTOR inhibitor (e.g. sirolimus or everolimus) have not been shown to have significant beneficial

Table 3 Management of BOS

- Exclude other, potentially treatable/reversible causes of impaired graft function
- Administration of chronic azithromycin
- Consider adjusting maintenance immunosuppression
 - Switch to tacrolimus if on CSA-based regimen
 - Avoid sustained, high-dose corticosteroids
- Evaluate for abnormal GER (acid and non-acid)
- Consider fundoplication if significant GER is present
- Consider IVIG, plasma exchange, and/or rituximab if de novo anti-HLA antigen detected
- Progressive BOS refractory to other interventions
 - Total lymphoid irradiation
 - Extracorporeal photopheresis
 - Retransplantation

CSA cyclosporine A; GER gastroesophageal reflux; IVIG intravenous immunoglobulin

effect [70]. However, a number of case series suggest that if a patient is not receiving tacrolimus as their calcineurin inhibitor, switching from CSA to tacrolimus may stabilize declining lung function [69, 71, 72]. If a significant level of one or more de novo anti-HLA antibodies is detected, intravenous immunoglobulin, plasmapheresis, and or anti-B-cell therapy (e.g. rituximab) may prove beneficial [70].

Azithromycin

Macrolides and neo-macrolides such as azithromycin (an azalide) possess anti-inflammatory effects and can inhibit IL-8 production and neutrophil recruitment, suppress bronchial inflammation, and prevent airway damage for a number of respiratory disorders [73]. Many centers have reported that a substantial number of patients who develop BOS respond to azithromycin and may have their lung function stabilized or significantly improve such that some patients may no longer meet FEV1 criteria for BOS as they respond to the drug [74, 75]. Notably, azithromycin has been reported to diminish the risk of graft loss and recipient death when given to patients with established BOS [20, 76]. The recently published, randomized prospective clinical trial conducted by Vos et al. [77] suggested that prophylactic administration of azithromycin initiated shortly after transplantation can significantly decrease the risk of developing BOS, although a significant impact on survival was not shown over the relatively brief, 2-year evaluation period.

Gastroesophageal reflux and (micro)aspiration

Abnormal GER is highly prevalent in patients with advanced lung disease and in LTX recipients [78, 79], and the

prevalence may increase post-transplant [80, 81]. Notably, abnormal acid GER has been strongly linked to risk for BOS. However, pharmacologic therapy with proton-pump inhibitors (PPI), although increased pH of gastric secretions induced by PPI therapy may relieve symptoms, may have little effect on GER [82]. It should be noted that the majority of studies in patients with advanced lung disease and LTX recipients only used pH monitoring and did not utilize impedance to detect weakly acid or non-acid reflux, which could contain bile acids, for one. Additionally, only recent studies have measured pepsin and bile acids in BAL fluid obtained at bronchoscopy, which can identify those patients in whom microaspiration of refluxed foregut secretions is actually taking place. Indeed, PPI therapy may have little effect on non-acid reflux, which typically contains bile acids that can be very injurious to the lung [82, 83]. Additionally, increased gastric pH induced by PPI therapy may allow some degree of bacterial overgrowth, and LPS from gram-negative bacteria, if present, may induce mucosal inflammation if aspirated [84]. Interestingly, non-acid reflux with bile acids has been linked to BOS and to chronic *Pseudomonas* colonization/infection [85], suggesting that bile acids aspirated into the lower respiratory tract may be particularly injurious to respiratory mucosae and induce airway injury and dysfunction consistent with BOS as well as chronic bacterial infection, which is also a risk factor associated with BOS. The situation can be complicated by the presence of significant esophageal motility disorders that are typical of patients with pulmonary fibrosis due to connective tissue disorders such as scleroderma [86], and aspiration of ingested foods may also lead to airway injury and BOS in LTX recipients. In addition to foregut dysmotility, swallowing disorders are not uncommon post-transplant [87], although the relationship of oropharyngeal dysphagia to BOS risk is unclear. Lastly, GER may promote autoimmune sensitization to self-antigens and increase risk of BOS via sensitization to collagen V [88].

Because pharmacologic suppression of gastric acid secretion may not significantly suppress abnormal GER (especially weakly acid or non-acid reflux) and microaspiration, gastric fundoplication has been investigated as means of preventing LTX complications and as a treatment for BOS when reflux appears to be present. A number of investigations have shown that fundoplication can be safely performed [89, 90, 91], and case series suggest that it may prevent the appearance of BOS or prevent its progression if abnormal GER is diagnosed in patients who have developed BOS [92]. Additionally, it may lead to improved lung function such that patients can revert to BOS Stage 0 [93], but prospective, randomized trials have not been reported. Interestingly, azithromycin therapy has been shown to decrease GER and microaspiration in lung transplant recipients [94], but it appears to have reduced efficacy when patients with BOS have evidence of bile acid aspiration [95], suggesting that fundoplication is likely the best approach to

managing GER in these patients, particularly if bile acids are present in BAL fluid.

Other therapies

Augmentation of immunosuppression via total lymphoid irradiation (TLI) or extracorporeal photopheresis (ECP) have been evaluated by a number of centers. These therapies attempt to reduce the numbers of sensitized lymphocytes that may be driving immunologically-mediated chronic rejection and causing BOS. Fisher et al. [96] reported significant reduction in the rate of FEV1 decline for 27 recipients who completed at least 80 % of the radiation fractions (pre-TLI 123 ml/month decline vs. 25 ml/month decline post-TLI); major adverse effects included bone marrow suppression and infection. Limited data suggest that ECP may reverse, stabilize or decrease the rate of FEV1 decline in some patients with BOS [97], but the mechanism of action is unclear. Postulated mechanisms to explain how ECP modifies host responses include induction of a clone-specific anti-lymphocyte immune response, altered cytokine production, and/or induction of regulatory T-cells. ECP is generally well-tolerated but expensive. Potential risks include infectious complications and/or bone marrow suppression. If bronchiectasis and chronic infection becomes established in recipients with evolving BOS, infections (e.g. *P. aeruginosa*) need to be treated and suppressed.

Retransplantation

Retransplantation may be the only treatment option for progressive BOS that is refractory to other forms of treatment. A number of single-center retrospective analyses have been reported, and actuarial survival has gradually improved [98, 99]. Outcomes after retransplantation appear to be better when performed for BOS versus outcomes for PGD or other complications, and outcomes following retransplantation for carefully selected patients (ambulatory patients evaluated via the same selection process used for first-time transplantation) with BOS are expected to approach those of first-time lung transplants if performed by experienced centers. Various ethical questions regarding access to the scarce resource of donor lungs (taking utility and equity into consideration) must be considered carefully when retransplantation is considered for refractory BOS or other allograft complications.

Prevention of BOS

It is generally agreed that LTX recipients should be maintained on triple immunotherapy in the form of a CNI (tacrolimus or CSA), an antimetabolite (mycophenolic acid or azathioprine) and corticosteroids (gradually tapered to low/minimal dose). The data for this is mostly derived from other forms of solid

organ transplantation. However, this approach is generally accepted for LTX recipients as it is well recognized that the lungs are the most immunogenic of the solid organs with a greater propensity for both acute and chronic allograft rejection. The best forms and combinations of maintenance therapy are unknown, but effective immunosuppression that can prevent AR, LB, or humoral rejection are essential. Many centers also administer an anti-lymphocyte antibody in the immediate post-operative period, although the impact on BOS incidence is marginal per the International Society for Lung Transplantation (ISHLT) Registry. An alternative to the antimetabolites are the mTOR inhibitors (sirolimus or everolimus), and a mTOR inhibitor can be used in their place or added to allow a decrease in calcineurin inhibitor dose. The calcineurin and mTOR inhibitors are metabolized by CYP3A4 (cytochrome P-450), and care must be taken to avoid drug-drug interactions if multiple CYP3A4-metabolized agents are used simultaneously. If pre-LTX anti-HLA antibodies are detected, cross-matching should be done to avoid implanting a mismatched allograft. Lastly, bronchial arteries are typically not re-anastomosed at the time of LTX, and it remains unknown whether re-establishing the bronchial circulation at the time of transplant can prevent subsequent BOS.

Rapid diagnosis and prompt/effective treatment of AR, LB, antibody-mediated rejection, or infection may not only prevent acute complications but also prevent the delayed appearance of BOS. Prevention of infection via prophylaxis (CMV, *Pneumocystis jiroveci*, *Aspergillus*) may also help prevent later BOS. Additionally, peri-operative targeted antibacterial therapy for bacterial isolates from respiratory secretions of patients with CF as well as non-CF recipients with bronchiectasis followed by sustained suppression (e.g. inhaled anti-pseudomonal antibiotics) may help prevent early untoward events but also diminish risk of delayed allograft dysfunction due to BOS. The prospective, randomized, placebo-controlled trial of azithromycin begun shortly after transplant suggest that such may prevent BOS/NRAD. However, whether LTX recipients should be placed on early azithromycin for BOS prophylaxis following successful LTX requires further investigation and discussion. If patients develop BOS and are not receiving azithromycin, available evidence strongly supports the initiation of chronic azithromycin therapy. Additionally, abnormal GER should be considered and ruled out via appropriate investigations. If GER is present, anti-reflux surgery (e.g. laparoscopic fundoplication) should be considered; if such surgery is indicated, it should be performed by a surgeon who is skilled in anti-reflux surgery.

New directions and research needs

Multicenter trials are needed to better establish optimal regimens for the induction and maintenance of immunosuppression

that can adequately prevent both acute and chronic allograft dysfunction yet not lead to excessive risk for infection or other untoward consequences. Testing that can identify patients who are more tolerant to their grafts and, therefore, require less intense immunosuppression is also needed. Induction of tolerance to self-antigens (e.g. collagen V) or strategies to augment regulatory T or B cells to promote and maintain tolerance may diminish risk for BOS. Guidelines for optimal testing for abnormal GER and the selection of patients (and procedure) for antireflux surgery to prevent or treat BOS need to be established, and, optimal approaches to allograft surveillance (e.g. the role of bronchoscopy with transbronchial biopsies in clinically stable LTX recipients, screening for de novo anti-HLA antibodies and the presence of humoral rejection) need to be determined. Finally, the effects of allograft cell senescence (accelerated aging) on allograft function and BOS risk need to be examined, and a better understanding of IL-17 and neutrophil responses as well as mechanisms by which EMT leads to airway fibrosis is needed. Placebo-controlled, preferably multicenter clinical trials that evaluate newer therapies to prevent or treat BOS (e.g. administration of pirfenidone, vitamin D supplemental, administration of montelukast or a combination of montelukast/azithromycin/inhaled corticosteroids as is used for bone marrow transplant recipients with OB, etc.) are needed.

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- of importance
- of major importance

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