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REVIEW

Chronic lung allograft dysfunction following lung transplantation: challenges and solutions

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Abstract: Chronic rejection is a major cause of death after the first year following lung transplantation. Bronchiolitis obliterans (BO) is the most common pathologic finding on biopsy, characterized by fibrous granulation tissue, which obliterates the lumen of the bronchiole. Clinically, in the absence of tissue for pathology, BO syndrome refers to a progressive irreversible drop in the forced expiratory volume in 1 second. Recently, a broader definition of chronic rejection, termed "chronic lung allograft dysfunction", has been used to encompass a more inclusive definition of posttransplant dysfunction. Recently, the lung transplant community has come to realize that chronic rejection may be the final common result after repetitive epithelial insults. Acute rejection, infection, and alloreactivity to mismatched HLA antigens are a few of these insults that damage the surface of the bronchioles. Recent evidence of autoimmunity to the normally hidden structural proteins collagen V and K-α1 tubulin have been correlated with a BO phenotype as well, perhaps correlating the epithelial damage with a mechanism for developing BO lesions. Many immunomodulatory medications and treatments have been studied for effectiveness for the treatment of chronic lung allograft dysfunction. New drugs, which more precisely target the immune system, are being developed and tested. Further study is required, but recent advances have improved our understanding of the pathogenesis and potential intervention for this common and deadly complication of lung transplantation.

Keywords: lung transplant, bronchiolitis obliterans syndrome, rejection

Introduction

Dr Bruce Reitz performed the first successful heart–lung transplants at Standford University (Stanford, CA, USA), in 1981, for idiopathic pulmonary hypertension and congenital heart disease.[1] Following this achievement, the first single-lung and double-lung transplant were performed by Dr Joel Cooper in Toronto, ON, Canada, in 1983 and 1986, respectively.[2] Beginning in the mid-1990s, the number of lung transplants has increased yearly to a total of 3,640 patients in 2011. From 1994 through 2011, the median survival of lung transplant recipients was 5.6 years. Improved survival early after lung transplant has resulted in better survival in the most recent era of lung transplantation. However, the slope of overall mortality after the first year during the most recent era mirrors that of previous eras. Following the first year, the most common causes of death are chronic rejection and non-Cytomegalovirus (CMV) infection.[3]

Chronic lung transplant rejection has classically been described as obliterative bronchiolitis (also called bronchiolitis obliterans [BO]). This was first described at Stanford in 1984. Of the 19 heart–lung transplants performed for end-stage pulmonary vascular disease, 14 patients were long-term survivors. Five of these patients demonstrated a

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typical initial restrictive ventilatory defect on spirometry, which improved over the first few months. However, this was followed by the development of a progressive obstructive ventilatory defect with a decline in the forced expiratory volume in 1 second (FEV_1). On biopsy, these patients had findings consistent with BO.[4]

BO develops in a nonuniform pattern and is difficult to sample bronchoscopically by transbronchial biopsy. Therefore, the clinical diagnosis of BO syndrome (BOS) is used to describe a progressive obstructive ventilatory defect without evidence of another explanation (acute rejection, infection, airway complication, or other cause). Recently, a paradigm shift has occurred in the thinking about chronic lung transplant rejection. Namely, BOS is now thought of as a large, but specific, form of chronic rejection. The term "chronic lung allograft dysfunction" (CLAD) has been introduced to include specific forms of allograft dysfunction (anastomotic stricture, azithromycin-responsive allograft dysfunction, disease recurrence, etc) in addition to a clinical description of both obstructive CLAD (BOS) and restrictive allograft syndrome (RAS) (Figure 1).[5]

Throughout this article, we will review the challenges inherent to the management of CLAD from diagnosis to understanding the pathogenesis and reducing risk factors. In addition, we will examine the available treatments for CLAD and their efficacy. This review will form a basic framework for understanding CLAD and discuss potential future solutions for reducing chronic rejection through new, more successful treatments.

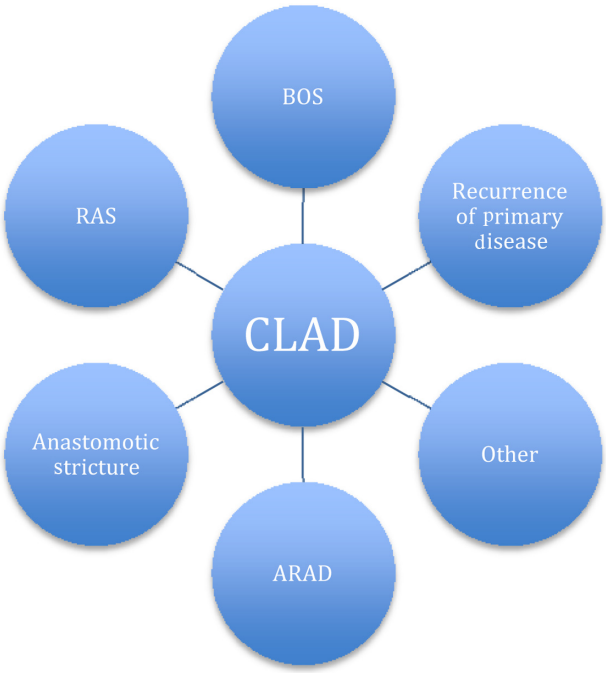

Figure 1 CLAD Phenotypes.
Notes: Chronic lung allograft dysfunction (CLAD) is a descriptive term for chronic lung transplant rejection which encompasses multiple different phenotypes, including bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS), recurrence of primary disease, anastomotic stricture, and azithromycin-responsive allograft dysfunction (ARAD), as well as other specific causes of decline in lung function.

BOS

BOS is the most common form of CLAD, accounting for approximately 70% of cases.[6] Pathologically, early BO is characterized by lymphocytic inflammation in the submucosa of respiratory bronchioles. This leads to late proliferation of dense fibromyxoid granulation tissue, which organizes to partially or completely fill the lumen of the airway (Figure 2).[7,8] On biopsy interpretation, these findings are denoted as "C1". These fibrotic lesions are thought to be the histologic result of repetitive epithelial injury by multiple different insults. However, obtaining sufficient histological specimens by transbronchial biopsy documenting these findings is unreliable.[9]

In the absence of histopathology from a biopsy specimen, BOS is more typically diagnosed on routine spirometry. In 1993, the International Society for Heart and Lung Transplantation (ISHLT) proposed criteria for the clinical diagnosis of BOS based on spirometry (Table 1). Measurements are made of post-transplant spirometry. When patients reach a baseline maximal FEV_1 (average of the two best measurements taken at least 3 weeks apart without administration of bronchodilators), this is termed "BOS Stage 0". Progressive decline in FEV_1 is staged as BOS 1 through 3, with a higher stage indicating a worsened obstruction. This schema was updated in 2001 to reflect new findings that a drop in FEV_1 and forced expiratory flow (FEF) 25%–75% is a more sensitive marker of early obstruction.[9,10] The new BOS stage 0p is defined as a decrease in the FEV_1 to $<90\%$ and a decrease in FEF 25%–75% to $\leq 75\%$ of the posttransplant baseline. It should be noted that, in children, by convention, the establishment of a reference value of lung function and subsequent decline are expressed in terms of percent predicted FEV_1.

Patients may present with nonproductive cough or dyspnea on exertion early in the course of BOS. However, patients frequently have few complaints, but an asymptomatic decline in their FEV_1 is discovered. In the more advanced stages of BOS, symptoms may progress to dyspnea at rest and productive cough with evidence of severe obstruction on spirometry. In an evaluation of health-related quality of life, Gerbase et al prospectively evaluated 58 patients and reported a decrease in the St George's Respiratory Questionnaire

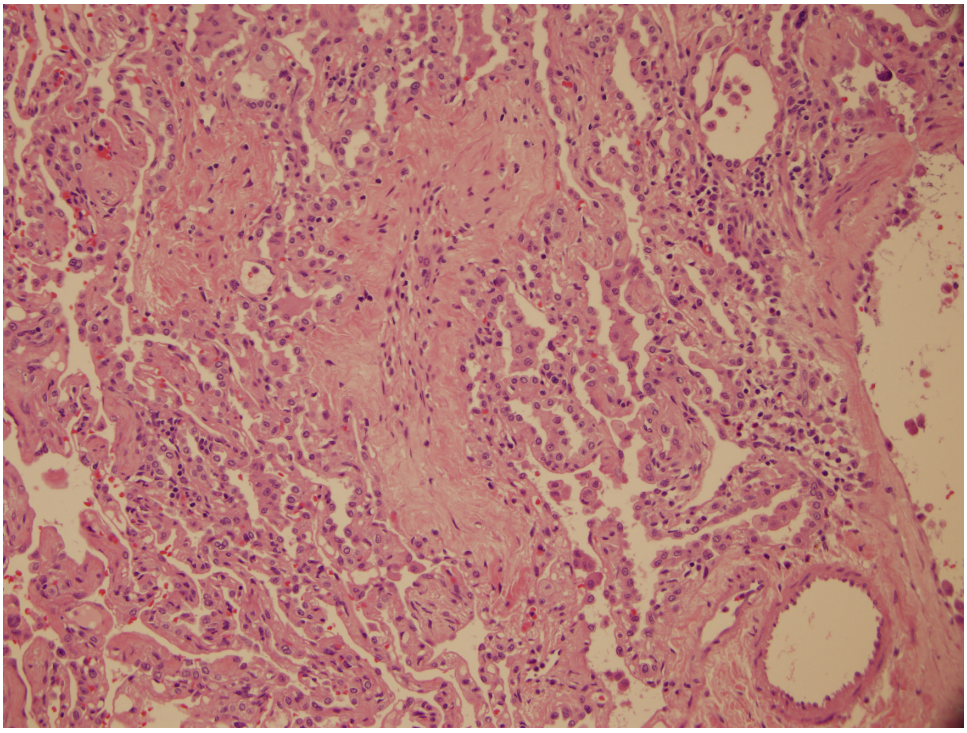

Figure 2 Lung biopsy showing bronchiolitis obliterans in the setting of chronic lung transplant rejection.
Notes: Hematoxylin and eosin stain was used.

(a standardized questionnaire used to measure health and perception of well-being[11]) among patients who developed BOS.[12] BOS is a major cause of both morbidity and mortality among lung transplant recipients. The most recent ISHLT data show that, 5 years after transplant, 49% of lung transplant recipients develop BOS, increasing to 76% at 10 years (Figure 3).[3] One retrospective analysis of actuarial survival placed the 3-year mortality after the onset of BOS at 51%.[13] Another study, from Denmark, showed a threefold increased risk of death after progression from BOS Stage 1 to Stage 2 and from BOS Stage 2 to Stage 3.[14]

When a lung transplant recipient is found to have a drop in their FEV_1, this should be investigated to determine if another cause is responsible. Typically, this includes chest radiography and bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies. The chest X-ray is not a useful tool for screening for early BOS, but is useful in establishing a differential diagnosis for the change in spirometry. Expiratory chest computed tomography reliably demonstrates air trapping and mosaic attenuation in patients with BOS.[15,16] However, when using the revised criteria to include BOS Stage 0p, which is more effective at early detection of BOS, thin-slice computed tomography was not helpful in making the diagnosis.[17] Bronchoscopy should be performed to rule out airway abnormalities and infectious causes of declining FEV_1. Aside from assessing

Table 1 BOS classification

Stage	1994 definition	2001 definition
BOS 0	FEV_1 ≥80% of baseline	FEV_1 >90% of baseline
		FEF 25%–75% >75% of baseline
BOS 0p		FEV_1 81%–90% of baseline
		FEF 25%–75% ≤75% of baseline
BOS 1	FEV_1 66%–80% of baseline	FEV_1 66%–80% of baseline
BOS 2	FEV_1 51%–65% of baseline	FEV_1 51%–65% of baseline
BOS 3	FEV_1 ≤50% of baseline	FEV_1 ≤50% of baseline

Abbreviations: BOS, bronchiolitis obliterans syndrome; FEF, forced expiratory flow; FEV_1, forced expiratory volume in 1 second.

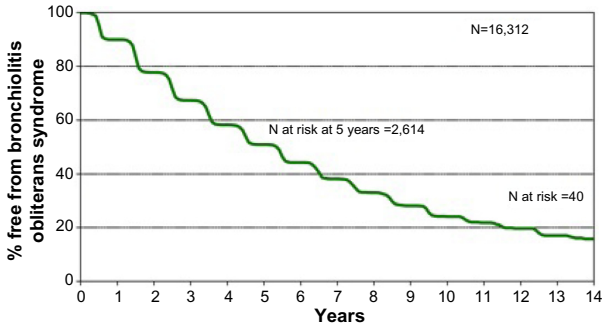

Figure 3 Adult lung transplant freedom from bronchiolitis obliterans syndrome conditional on survival to 14 days (April 1994–June 2012).
Notes: Reprinted from *J Heart Lung Transplant*, 32(10), Yusen RD, Christie JD, Edwards LB, et al; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung And Heart-Lung Transplant Report – 2013; focus theme: age, 965–978, Copyright 2013, with permission from Elsevier.[3]

infection, the BAL fluid has been studied to determine its utility in predicting onset of BOS. In a retrospective study, BAL neutrophilia ≥20% was a significant predictor for BOS Stage 1 or greater in a multivariate regression model. Neurohr et al also demonstrated increased IL-8 levels and reduced secretory leukocyte protease inhibitor (SLPI) within the BAL fluid. These markers were present independent of airway bacterial colonization.[18] Other studies have demonstrated elevated levels of other cytokines and inflammatory proteins, such as MPO, IL-12, and IL-17; however, it is unclear what predictive value these or the presence of airway neutrophilia have in the diagnosis of BOS due to multiple possible confounding factors.[19–21]

RAS

While BOS is the most common form of CLAD, increasing recognition of a restrictive form of chronic rejection has been reported by several centers. This restrictive ventilatory defect has been termed "RAS". The initial report by Sato et al, a retrospective review, reports their experience over a 13-year period. Patients were screened for CLAD by routine spirometry and diagnosed when their FEV_1 declined to <80% of previous baseline. RAS was diagnosed when a follow-up total lung capacity (TLC) measurement declined to <90% of baseline. Of the 156 episodes of CLAD diagnosed, 47% were characterized as RAS. Patients with RAS had a higher incidence of CMV mismatch but were otherwise similar regarding donor age, recipient age, primary diagnosis, and sex. Most notably, Sato et al discovered that patients with RAS had a median survival that was less than half that of BOS (541 days versus 1,421 days).[6] This definition of RAS was limited to bilateral lung transplant recipients only.

These investigators evaluated the progression of RAS in a separate study. During this retrospective review, they found that RAS, unlike BOS, was characterized by sporadic acute exacerbations and a stepwise decline in FEV_1 over time. Patients primarily presented with symptoms of shortness of breath, fever, and cough during an acute exacerbation. The patients they studied had between one and four exacerbations, after which they did not recover to their baseline FEV_1. Their outcomes included 32% of patients that had a partial recovery, 27% that had stable disease, and 41% that had progressive disease. Radiologic findings during acute exacerbation were principally characterized by asymmetric bilateral ground-glass opacities. However, during the period between acute exacerbations, interstitial reticular shadows, consolidation, and traction bronchiectasis were more often present.[22]

While definitive pathologic findings have not been thoroughly described, initial work from Toronto has demonstrated consistent findings within the cohort of RAS patients described previously. Of the 47 patients diagnosed with RAS, 16 had histopathologic specimens available for examination. Fifteen of these sixteen had findings of parenchymal fibroelastosis in a subpleural distribution. There were often coincident findings of BO and diffuse alveolar damage.[23] Diffuse alveolar damage was the predominant histopathologic finding within the acute exacerbation group described previously.[22] As a newly described phenomena, the characterization of RAS continues to evolve, but it undoubtedly represents a significant and potentially severe posttransplant complication.

Risk factors for the development of CLAD

Initially, after BOS was recognized to be a major contributor to posttransplant mortality, work began to determine what factors increased the risk of developing this progressive and, in many cases, untreatable complication. In 1998, a report from Heng et al did not show any relation to sex, age, primary disease, or graft ischemic time. Early acute rejection, CMV status, pulmonary infection, organizing pneumonia, and human leukocyte antigen (HLA) mismatch seemed to be significantly associated with onset of BOS.[13] A common thread among these risk factors may be the immune system's exposure to injured pulmonary epithelium. It has been hypothesized that this injury response via alloimmune and autoimmune mechanisms could play a major role in the development of BOS. Further delineation of the major risk factors for BOS, proposed underlying mechanisms of injury, and the immune system response will be reviewed here.

Acute cellular rejection

An early retrospective investigation by Bando et al identified, by multivariate analysis, that three or more episodes of acute cellular rejection graded mild to moderate (grade II to III, or A2 to A3) or greater significantly increased the risk of developing BOS.[24] Kroshus et al also showed that the cumulative number of episodes of acute rejection after 90 days increased the relative risk of BOS.[25] While these analyses showed that moderate-to-severe rejection and multiple episodes of rejection were risk factors for BOS, Hachem et al[26] found that even a single episode of early or late minimal (A1) acute cellular rejection was associated with a hazard ratio (HR) of 2.64 for the development of BOS 1 stage. Khalifah et al showed that

a single episode of A2 was associated with more frequent progressive BOS.[26] Recent work from San Segundo et al has demonstrated that an increased number of peripherally circulating CD8+ effector T-cells, both pre-transplant and during the first year after lung transplant, is associated with a higher risk of developing acute rejection.[28] Additionally, T-cell activity, in the form of granzyme B production and other cytokine profiles, has been shown to be elevated in lung recipients with acute rejection and prior to or at onset of BOS, leading to the concept that physiologic measurements and assessments of T-cell function may be a better way of monitoring the level of immunosuppression in lung recipients than the current method of adjusting medications based on serum drug levels.[29,30]

Lymphocytic bronchiolitis

In 1992, Yousem described submucosal lymphocytic and plasma cell infiltration around the airways and deep to the smooth muscle layer, which was called lymphocytic bronchitis and bronchiolitis (LBB, or B-grade) (Figure 4). This lymphocytic infiltrate was present more commonly in patients who later went on to develop BO.[31] Husain et al showed that LBB was, similarly to acute perivascular rejection, associated with onset of BOS. At 1 year, patients who went on to develop BOS had over twice as many episodes of LBB as did those without BOS.[32]

CMV infection

CMV infection is a common infectious complication in the posttransplant period in patients with both reactivated or donor-derived CMV infection. An initial study by Keenan et al, from Pittsburgh, PA, USA, associated BOS with pre-transplant seropositive status, seropositive donor status, and posttransplant CMV infection.[33] Further work by Smith et al found that CMV mismatch (donor positive/recipient negative) may be a risk factor for developing BOS within 3 years of transplantation.[34] However, other groups have found diverging data regarding the risk of BOS based on CMV serostatus and infection.[35–37] Tamm et al reviewed their center's experience with CMV pneumonia and CMV serostatus, finding no significant differences in development of BOS, and suggested that treatment of CMV pneumonia with intravenous ganciclovir is protective.[38] When ganciclovir is ineffective, such as in cases of ganciclovir-resistant CMV, an earlier onset of BOS has been reported.[39]

Non-CMV infections

While CMV pneumonitis is perhaps the most consistently implicated infection in the development of BOS, multiple studies have evaluated whether other infections are significant risk factors. An early study by Hohlfeld et al found that 47% of the onset of BOS seemed to cluster in the first quarter of the year, January to March, suggesting a possible relationship

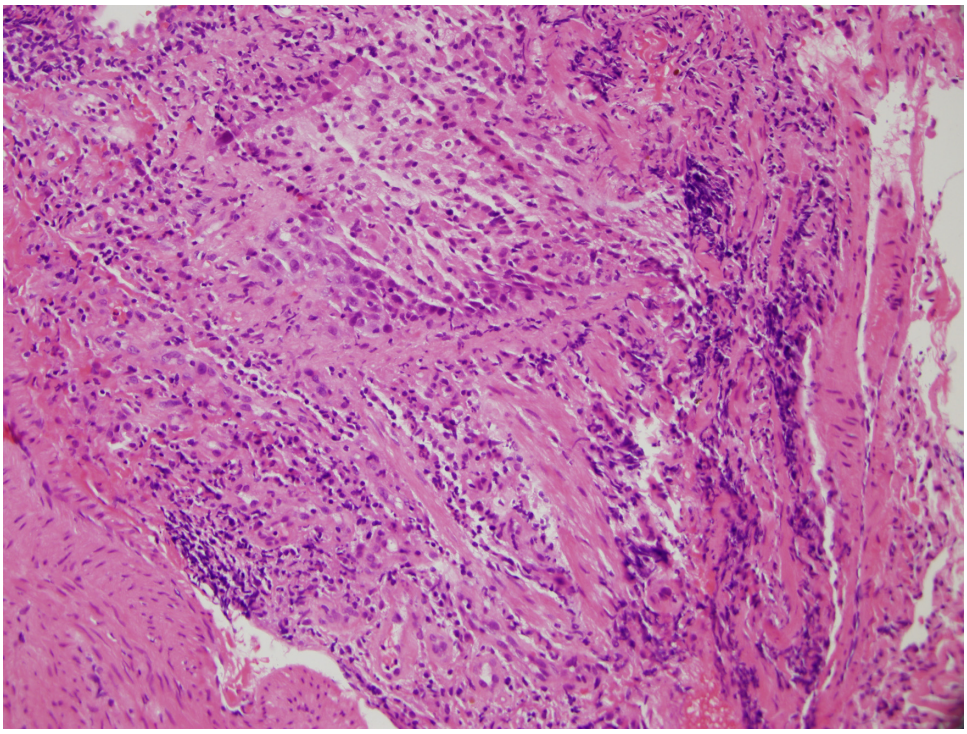

Figure 4 Lung biopsy showing lymphocytic bronchiolitis in the setting of acute lung transplant rejection.
Notes: Hematoxylin and eosin stain was used.

with viral infections.[40] Community-acquired respiratory viruses ([CARVs] including rhinovirus, coronavirus, respiratory syncytial virus, parainfluenza, human metapneumovirus, influenza A and B, and adenovirus) have been implicated in the development of BOS.[41,42] Kumar et al[42] reported that of nine of 50 patients with a decline in FEV_1 after CARV infection, six had persistent disease classified as BOS. In a retrospective review by Khalifah et al, 259 consecutive lung transplant patients were found to have 21 episodes of CARV infection, which were associated with an HR of 2.05 for development of BOS Stage 1, and lower respiratory tract involvement increased the HR to 3.03.[43] This was verified prospectively in a mouse model using orthotopic tracheal transplant.[44] In one series, 0 of 18 patients developed BOS after treatment with intravenous ribavirin, suggesting that treatment of CARV could prevent the onset of chronic rejection.[45] Other viruses, such as Epstein–Barr virus and human herpes virus-6, have also been implicated in the development of BOS, though with less supporting evidence.[46,47]

In addition to viral infection, bacterial and fungal infections predispose patients to increased rates of BOS as well. Valentine et al published their experience, finding that Gram-negative, Gram-positive, and fungal pneumonias all significantly increased the risk for BOS. In fact, compared with uninfected patients, those with bacterial pneumonia and fungal pneumonia developed BOS 6 months and 2 years earlier, respectively.[48] Further, not just infection, but colonization of the airways seems to be a significant risk factor for the development of BOS. Botha et al found that *Pseudomonas aeruginosa* colonization of the airways in lung transplant recipients increased the risk of BOS at 2 years from 7.7% to 23.4%.[49] Similarly, Weigt et al examined the effect of *Aspergillus* spp. colonization on the incidence of BOS. Using a multivariate analysis, *Aspergillus* colonization was independently associated with onset and mortality due to BOS.[50]

Primary graft dysfunction (PGD)

PGD is a common early complication after lung transplantation manifested by infiltrates that can be seen on chest radiograph and impairment of oxygenation. Whitson et al showed that PGD grade 3 (bilateral infiltrates and PaO_2/FiO_2 <200 mmHg) was associated with BOS and a consistently lower FEV_1 at all time points in bilateral lung transplant recipients.[51] In a retrospective review, Daud et al found that PGD was significantly associated with onset of BOS independent of acute rejection, lymphocytic bronchiolitis, and CARV. With increasing grade of PGD, there was a progressive increase in relative risk for development of BOS (PGD grade 1=1.68, grade 2=2.04, grade 3=2.61).[52]

Gastroesophageal reflux (GER)

D'Ovidio et al investigated the hypothesis that GER could be a contributing factor for development of BOS. Using esophageal pH <4, they showed that patients with abnormal pH had an increased rate of BOS. In addition, they correlated presence of bile acid and subsequent decreased levels of surfactant protein A in the BAL fluid.[53] Blondeau et al[54] found that both pepsin and bile acid were routinely found in the BAL of lung transplant recipients. However, they did not find a correlation with GER, but instead an association with both acid and non-acid reflux, suggesting this could be the true risk factor for BOS. In a single center study, Cantu et al described a strategy for surgical treatment, via fundoplication, for lung transplant patients. At their center, all transplant candidates are screened with esophageal pH monitoring and surgery is performed posttransplant for any patient with evidence of reflux and without a contraindication. Their retrospective review evaluated the results of these efforts over time. Of 202 patients screened for reflux, 85 had either early (average time after transplant =43 days) or late (average time after transplant =684 days) surgical treatment aimed at control of reflux. Freedom from BOS at 1 year was observed in 100% of those with early surgery (n=14), compared with 91% of those without reflux (n=180) and 92% of those in the late surgery group (n=62). At 3 years, that difference was greater: freedom from BOS was 100% in the early surgery group (n=5), compared with 62% in those without reflux (n=93) and 47% in the late surgery group (n=30).[55] The benefit of surgical correction of GER in asymptomatic lung transplant recipients is an ongoing area of investigation; there remains no consensus between transplant centers on the use of fundoplication for GER in lung recipients. The preliminary data from the multicenter Reflux Surgery in Lung Transplantation (RESULT) study was presented at the ISHLT meeting in April 2014 and, at that time, did not reveal any significant benefit to fundoplication. The final report of this study is pending at this time.[56]

HLA mismatching

Given the hypothesis of alloimmune activation as a primary cause for CLAD, HLA mismatch between donor and recipient has been extensively studied. Previous studies in heart and kidney transplantation revealed that HLA mismatch was a significant risk factor for graft loss.[57,58] Single-center studies revealed an association between both HLA class I (HLA-A)

and class II (HLA-DR) mismatches and development of BOS.[59,60] A large, United Network for Organ Sharing (UNOS)/ISHLT database study revealed a significant increase in the risk of acute rejection and graft failure associated with HLA-A and HLA-DR, but, due to limited follow-up, did not find a significant increase in the rate of BOS.[58] Many other contradictory studies, which make this risk less clear, have also been published.[13,35,60]

The evidence is more consistent in the study of anti-HLA antibodies that develop posttransplant. Sundaresan et al showed this was a much stronger signal for development of BOS than HLA-A mismatch at the time of transplantation.[59] These results have been duplicated as well.[61] Improvement in the sensitivity of diagnostic techniques has allowed for better detection of anti-HLA antibodies and increased ability to correlate those results with BOS.[62] Previous work by Jaramillo et al has demonstrated that anti-HLA class I antibodies trigger the activation and proliferation of airway epithelial cells as well as production of growth factors, fibroblast proliferation, and apoptosis.[63]

Further work by Hachem et al examined the development of donor-specific anti-HLA antibodies (DSA) in a single-center prospective trial. Of the 116 patients examined, 56% developed DSA (15% class I, 63% class II, 22% both classes). This study was designed to examine the effect of treatment for DSA with either intravenous immunoglobulin (IVIG) or IVIG plus rituximab on the development of antibody-mediated acute and chronic rejection. They found that, irrespective of the treatment received, patients that cleared their DSA after treatment had a lower incidence of BOS and prolonged survival compared to those with persistent DSA.[64] Newer modalities of therapy for antibody-mediated rejection and depletion of anti-HLA antibodies have been studied more extensively in kidney transplantation, including bortezomib, a 26S proteasome inhibitor that can block NF-κB signaling within mature plasma cells.[65]

Non-HLA autoimmune response

In addition to the alloimmune response to donor HLA, increased risk of BOS due to a similar autoimmune response has been observed in non-HLA antibodies such as collagen V and K-α1 tubulin.[66,67] Specifically, these anti-airway epithelial cell antibodies have been found in up to 31% of lung transplant recipients with BOS. Downstream signaling via increased calcium influx leads to cell proliferation and increased transcription of fibrogenic growth factors, similar to the anti-HLA response.[68] This autoimmune activation seems to be mediated by a Th17 response.[69] Other labs have also shown that a failure of maturation of regulatory T cells may contribute to the autoimmune reaction seen in chronic lung transplant rejection.[70]

Treatment

Typical immunosuppression for lung transplant recipients includes a calcineurin inhibitor, a purine synthesis inhibitor, and a corticosteroid. Based on the major risk factors for CLAD identified to date, it is clear that immunosuppression plays a major role in its prevention. Aside from ensuring adequate dosing and blood levels of immunosuppressive drugs, a switch between these drugs has been shown to potentially treat BOS. In one of the first trials to assess the change in pulmonary function when switching from cyclosporine to tacrolimus, Cairn et al showed that, in patients with BOS, the rate of decline in FEV_1 and FEF 25%–75% decreased significantly in the 70% of patients that responded.[71] Hachem et al conducted a randomized controlled trial to evaluate the outcomes after treating patients with one of the calcineurin inhibitors, either cyclophosphamide or tacrolimus. There was a nonstatistically significant decline in the occurrence of BOS in the tacrolimus group compared to the cyclosporine group.[72] Similar stabilization of spirometry has also been shown when switching from azathioprine to mycophenolate mofetil.[73] Other immunosuppressive agents, such as methotrexate and cyclophosphamide, have also been studied in small case series with successful stabilization of FEV_1.[74,75] However, given their potentially severe side effects, they have not gained wide acceptance.

Aerosolized cyclosporine and tacrolimus have also been studied to try to maximize drug delivery to the lungs while minimizing toxicity.[76–78] Initially, cyclosporine was studied as a means of reducing acute rejection; however, Iacono et al noted increased chronic rejection-free survival instead.[78] The follow-up study by Groves et al, which randomized patients to inhaled cyclosporine versus inhaled placebo, determined that, in addition to standard immunosuppression, inhaled cyclosporine yielded improved FEV_1 and FEF 25%–75%.[76]

The macrolide antibiotic azithromycin has been extensively studied for the treatment and prevention of CLAD. An initial pilot study of six patients demonstrated that, after initiation of azithromycin, five of six had improvement in FEV_1 of approximately 17% of predicted values.[79] Yates et al used azithromycin to treat BOS in 20 patients, resulting in a mean improvement in FEV_1 of 110 mL at 3 months. This improvement was maintained in 12 of the 17 patients that showed initial improvement.[80] Further evidence suggests that a survival advantage is obtained when starting azithromycin

during BOS Stage 1, rather than BOS at stages higher than Stage 1.[81] Attempting to determine a predictive model in which patients will benefit from azithromycin therapy, Verleden et al found that responders had a significantly higher pretreatment BAL neutrophilia and elevated IL-8 mRNA levels.[82] Azithromycin has also been investigated for prevention of BOS in a randomized controlled trial at the Leuven University Hospital (Leuven, Belgium). Over 2 years, BOS occurred less frequently in those on azithromycin (12.5%) versus those on placebo (44.2%).[83]

Newer antiproliferative agents such as sirolimus and everolimus have been investigated for their unique mechanism of action. Typically, they are substituted for azathioprine, as in the study by Hachem et al, who made the substitution after patients developed a composite endpoint of cumulative acute rejection, lymphocytic bronchiolitis, or BOS.[72] While these patients had a decrease in their cumulative acute rejection score, they did not have less incidence of lymphocytic bronchiolitis or BOS. In fact, approximately 60% of patients had to discontinue therapy due to adverse reaction. In another study, Roman et al found improved renal insufficiency but no change in FEV_1 in patients who were converted to everolimus from either a calcineurin inhibitor or a purine synthesis inhibitor.[84]

Immunodepleting and cytotoxic therapies have also been investigated. Anti-thymocyte globulin, which depletes circulating T-cells, was found to slow the decline of FEV_1 over the first 3 months after treatment. However, in all but two cases, BOS ultimately progressed.[85] Alemtuzumab, an anti-CD52 antibody, was studied in the setting of refractory acute rejection by Reams et al. CD52 is a surface protein expressed on B-cells, T-cells, monocytes, macrophages, and platelets. Their study observed ten patients with BOS who had previously failed increased prednisone and anti-thymocyte globulin. Four of the ten patients had improved FEV_1. However, during the study, 73% of patients experienced an infectious complication.[86]

While medications to modify the immune system represent the majority of the treatments that have been used for BOS, certain procedures to modify the immune system have also been studied. One such therapy is extracorporeal photopheresis (ECP). This procedure involves administering 8-methoxypsoralen, performing leukapheresis through an extracorporeal circuit, exposure of these leukocytes to ultraviolet A light, and infusing the leukocytes back into the patient. DNA in the leukocytes is cross-linked by the ultraviolet A light, though this only affects 2%–5% of the peripheral leukocytes per treatment. Other proposed mechanisms by which ECP works include a release of inflammatory mediators, apoptosis of peripheral T-cell populations, and, most importantly, the production of a suppressor T-cell response and induction of immune tolerance.[87] Preliminary reports showed that ECP can stabilize the decline in FEV_1 in some patients who were refractory to all other available treatments.[87,88] Based on reports from Meloni et al, responders to ECP tend to have increased circulating T-regulatory cells in response to treatment.[89] In the largest study to date, Morrell et al[1] showed that, after initiation of ECP, rate of decline in FEV_1 slowed and stabilized with minimal related complications. Other nonpharmacological therapies, such as total lymphoid irradiation, were initially successful in small series of patients, but there was significant drop out due to progressive BOS or bone marrow suppression.[90,91]

Treatments for RAS mirror the treatments for BOS descried as above. While understanding of the risk factors and underlying immune response for BOS has slowly progressed, the questions regarding the etiology of RAS are even more numerous. In initial studies, neither augmented corticosteroids nor antibiotics showed improved survival for patients with RAS.[22] Other investigators have attempted to use drugs being investigated for pulmonary fibrosis, such as pirfenidone, for treatment, with little success.[92]

The last line of treatment for refractory CLAD is repeat lung transplantation. However, ethical questions regarding the appropriateness of retransplantation in the setting of large waiting lists for first-time transplantation have been raised. In addition, early data from a pulmonary retransplant registry showed worse survival and earlier onset of BOS compared with first-time lung transplants.[1,93] More recently, Hayes reviewed analyses of retransplantation and found a comparable 1-year and 5-year survival rates.[94] The role of retransplantation as a treatment for chronic lung allograft dysfunction remains controversial and policies vary by center on the frequency of its use.

Conclusion

CLAD is the most common cause of death among lung transplant recipients after the first year. Through 3 decades of experience, the rate of mortality within the first year after transplantation has decreased. While there are still many unanswered questions regarding the development of chronic lung transplant rejection, recognition of subgroups within CLAD allows more specific pathophysiologic investigations and the potential to develop effective treatment modalities for patients as we begin to practice precision medicine. With the knowledge accumulated over time, the major risk factors for the development of chronic rejection have been clarified,

a greater understanding of the immunobiology related to the progression of CLAD has been achieved, and new immunomodulatory treatments have been developed to take advantage of knowledge gained. We can imagine that, in the decades to come, CLAD will become better understood and that newer, more precise therapies will be implemented, allowing lung transplant recipients to enjoy longer survival than those lung recipients who have gone before them.

Disclosure

The authors report no conflicts of interest in this work.

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