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CHEST Translating Basic Research Into Clinical Practice

Bronchiolitis Obliterans Syndrome

The Final Frontier for Lung Transplantation

Jamie L. Todd, MD; and Scott M. Palmer, MD, MHS, FCCP

Bronchiolitis obliterans syndrome (BOS) is a form of chronic lung allograft dysfunction that affects a majority of lung transplant recipients and is the principal factor limiting long-term transplant survival. BOS is characterized by progressive airflow obstruction unexplained by acute rejection, infection, or other coexistent condition. Although BOS is a proven useful clinical syndrome that identifies patients at increased risk for death, its clinical course and underlying causative factors are now recognized to be increasingly heterogeneous. Regardless of the clinical history, the primary pathologic correlate of BOS is bronchiolitis obliterans, a condition of intraluminal airway fibrosis. This article highlights the body of developing research illustrating the mechanisms by which BOS is mediated, including alloimmune reactivity, the emerging roles of humoral and autoimmunity, activation of innate immune cells, and response to nonimmune-related allograft insults, such as infection and aspiration. In addition, we underscore emerging clinical implications and promising future translational research directions that have the potential to advance our knowledge and improve patient outcomes. ***CHEST 2011; 140(2):502–508***

Abbreviations: BO = bronchiolitis obliterans; BOS = bronchiolitis obliterans syndrome; col(V) = type V collagen; DAMP = damage-associated molecular pattern; DSA = donor-specific antibody; HLA = human leukocyte antigen; IVIG = IV immunoglobulin; LPS = lipopolysaccharide; PAMP = pathogen-associated molecular pattern; PRR = pattern recognition receptor; Th = T helper; TLR = toll-like receptor

Bronchiolitis obliterans (BO) was first recognized in the mid-1980s as a form of chronic lung allograft dysfunction among a small cohort of heart-lung transplant recipients at Stanford University.[1] Histologically, it is characterized by patchy submucosal fibrosis involving the respiratory bronchioles, resulting in near-total or total occlusion of the airway lumen (Fig 1). Given the nonuniform distribution of fibrosis and involvement of airways that are not well sampled by transbronchial biopsy, BO syndrome (BOS) is clinically defined as progressive airflow obstruction unexplained by acute rejection, infection, or other confounding complication.[2] As in the Stanford cohort, this deterioration in pulmonary function generally is irreversible and progresses despite a number of empirical therapies, including augmented immunosuppression.

Unfortunately, many years after its initial description, BOS remains a pervasive process with devastating consequences. In excess of 50% of patients surviving to 5 years after transplantation will develop BOS (Fig 2).[3] Its onset is associated with poor survival, and this mortality impact is even more pronounced in those who develop BOS within 2 years of transplantation (hazard ratio, 1.84; 95% CI, 1.03-3.29).[4] Gains in health-related quality of life achieved with lung transplantation also are curtailed by the development of BOS.[5,6] Despite rapid advances in the discipline of lung transplantation and demonstrable improvement in short-term outcomes,[3] there has been no substantial decrease in the prevalence of BOS, and no effective treatment has yet been established. As such, BOS is the principal factor contributing to

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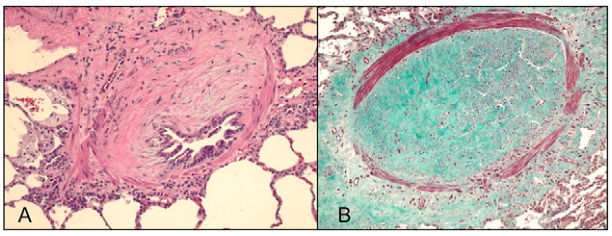

FIGURE 1. A, Explanted lung tissue taken from a patient with bronchiolitis obliterans syndrome (BOS) demonstrating the pathologic lesion of bronchiolitis obliterans (BO) with near-total occlusion of a small airways lumen. Some normal-appearing bronchial epithelium remains (hematoxylin-eosin, original magnification × 10). B, Explanted lung tissue taken from a patient with BOS demonstrating advanced BO with complete fibrous obliteration of the airway lumen (Masson trichrome stain, original magnification × 10).

limited long-term survival and suboptimal quality of life among lung allograft recipients and represents a major scientific challenge that must be surmounted before lung transplantation can become a durable, curative therapy for patients with advanced lung disease.

Increasingly, the lesion of BO is thought to represent the shared histologic outcome of injury to the airway epithelium and subcellular matrix by an array of immune and inflammatory insults. From a clinical standpoint, however, BOS remains heterogeneous, varying both in its timing of onset after transplantation and in the aggressiveness of its clinical course. What accounts for this significant interindividual variation is not fully explained, but it is likely related to the range of insults and immunologic mechanisms underlying the pathogenesis of BOS, as described later in this article, in addition to the timing and extent to which these insults occur and mechanisms become activated in an individual patient.

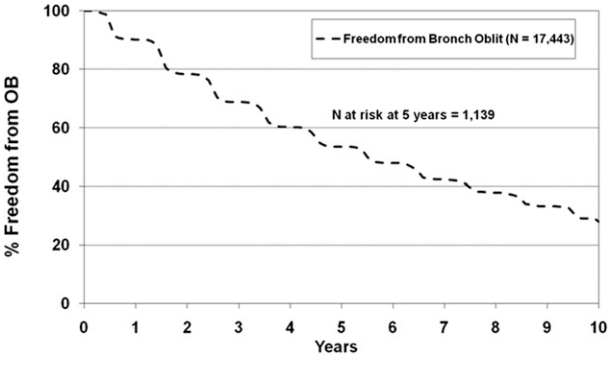

FIGURE 2. International registry data indicating freedom from BOS in adult lung allograft recipients for follow-up between April 1994 and June 2007, conditional on survival to 14 days. Bronch Oblit = bronchiolitis obliterans; OB = obliterative bronchiolitis. See Figure 1 legend for expansion of other abbreviation. (Adapted with permission from Christie et al.[3])

MECHANISMS OF PATHOGENESIS AND RELATED CLINICAL IMPLICATIONS

Alloimmune T-Cell Reactivity

The rarity of BO in patients without transplantation emphasizes the fundamental role of alloimmune T-cell reactivity in the development of this condition. Acute cellular rejection is the most consistently described risk factor for BOS. Specifically, both acute vascular (A-grade) rejection, especially if histologically severe,[7] and lymphocytic bronchiolitis (B-grade) rejection are associated with a significantly increased risk of BOS.[8] Animal tracheal transplantation models demonstrate lymphocytic airway inflammation that reproduces the bronchiolitis seen in humans. In these models, the initial alloimmune response is of the T helper (Th) 1 type, with interferon-γ being the predominant cytokine.[9] Interferon-γ upregulates the expression of adhesion and costimulatory molecules by airway epithelial cells, thus further augmenting the alloimmune response by stimulating lymphocyte infiltration and priming T-cell responses.[10] The airway epithelial cell itself, once activated, generates a profibrotic milieu, producing growth factors that ultimately result in tracheal obliteration.[11] The presence of obliterative disease in allogeneic, but not syngeneic, tracheal transplantations supports the importance of alloimmunity in airway fibrosis.[12]

Attenuating alloimmune T-cell-mediated damage to the lung allograft, therefore, should reduce bronchial epithelial injury and the fibroproliferative events that ensue. Unfortunately, BO occurs despite intensive T-cell-based therapies administered throughout the lifetime of a transplantation recipient. More recently, novel therapies aimed at even more aggressive T-cell depletion have been evaluated in small cohorts of patients with BOS. Alemtuzumab, an anti-CD52 antibody, has generated interest both as an induction agent[13] and as a therapeutic agent and was shown to stabilize or improve pulmonary function in a small number of patients with BOS who had not responded to conventional rejection treatments with antithymocyte globulin or methylprednisolone.[14]

Others have hypothesized that direct aerosol delivery of calcineurin inhibitors to the lower respiratory tract could increase drug concentrations in the allograft and as such, reduce acute rejection or BOS while minimizing concerns of systemic toxicity. A randomized controlled trial of aerosolized cyclosporine given daily for the first 2 years posttransplantation, concurrent with a tacrolimus-based immunosuppressive regimen, improved BOS-free survival in the treatment group compared with the placebo group but somewhat surprisingly had no effect on acute rejection rates.[15] Although replication of these results is

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needed in a larger multicenter cohort, this approach represents a promising new drug delivery mechanism in lung transplantation recipients.

Despite clinical and basic evidence supporting a central role for alloimmune reactivity in the development of BOS, the failure of T-cell-based immunosuppressive regimens to prevent the onset of BOS or stabilize lung function after its onset supports the importance of other mechanisms of disease pathogenesis. Indeed, recent work has elucidated several additional immune- and nonimmune-related mechanisms that likely contribute to the high burden of BO after lung transplantation. Clearly, increased understanding of these factors is critical to the development of improved approaches to prevent and treat BOS.

Humoral Immunity

Recognition of the role of humoral, or antibody-mediated, processes in the pathogenesis of BOS has had a substantive impact on the clinical approach to its prevention and treatment. Laboratory advancements in the detection and characterization of human leukocyte antigen (HLA) antibodies by flow cytometry (reviewed in detail elsewhere[16]) in conjunction with tissue immunostaining for complement fixation have provided clinical evidence that antibody-mediated rejection occurs in lung transplantation.[17] In particular, independent reports from several centers now suggest that the development of posttransplant HLA antibodies in lung transplant recipients is correlated with an increased risk for BOS and worse overall survival.[18-20] Basic research findings support the concept that alloantibodies potentiate airway fibrosis. Jaramillo and colleagues[21] demonstrated that airway epithelial cells cultured with class 1 HLA antibodies become activated, stimulate fibroblast proliferation, and ultimately undergo apoptosis. The group later translated this work to an in vivo system. Class 1 HLA antibody instillation into the trachea of a murine host resulted in epithelial cell hyperplasia, fibrosis, and obliteration of the small airways, resembling human BO.[22]

Non-HLA antibodies targeted at the bronchial epithelium and bronchial wall microvasculature also have been detected and described among lung allograft recipients.[17,23,24] Jaramillo et al[24] noted that the development of a de novo non-HLA antibody directed at an antigen on the airway epithelial cell membrane preceded the onset of BOS in a small cohort of patients. The authors further detailed that upon binding to its antigen, the antibody induced epithelial cell proliferation and transcription upregulation of profibrotic cytokines. Although there is currently no standardized, available assay by which to detect these antibodies in the clinical setting, their description suggests that antigenic targets of the humoral immune response in BOS extend beyond that of primary alloantigens.

B-cell-modulating therapies are now being used to reduce the humoral immune response in lung transplant recipients who develop donor-specific HLA antibodies in an effort to decrease the occurrence or progression of BOS. This treatment can have the benefit of being preemptive when given prior to the onset of acute rejection or BOS in patients with donor-specific antibody (DSA). Hachem et al[25] recently published a prospective observational study in which a protocol to routinely screen for and subsequently treat DSA with IV immunoglobulin (IVIG), rituximab, or both was implemented. Although a randomized controlled study is needed to assess optimum drug and dosing regimens, these preliminary data show that patients in whom drug treatment resulted in successful alloantibody clearance had improved freedom from BOS and survival than those who had persistent detectable alloantibody. Furthermore, the combination of rituximab and IVIG appeared to be more effective than IVIG alone.[25]

Novel humoral immune-modulating agents are just beginning to be explored in solid organ transplantation. Bortezomib, an inhibitor of the 26S proteosome, has proven useful in the reversal of alloantibody-mediated rejection in renal transplantation recipients.[26] Even more intriguing, recent data from an animal model of chronic cardiac allograft rejection demonstrated a reduction in chronic vasculopathic lesions in those treated with bortezomib.[27] Bortezomib is unique when compared with IVIG and rituximab because it specifically targets antibody-producing mature plasma cells and, therefore, may more effectively eliminate DSA.[26] Its use currently is being expanded to lung transplant recipients, with initial promising results[28]; however, further translational and clinical research is warranted to clearly define the safety and potential benefits of this highly potent, targeted therapy.

Autoimmunity

The discovery of autoimmunity as a mediator of BOS is one of the most exciting novel cellular mechanisms recently described. Sumpter and Wilkes[29] have developed the concept that rejection is biphasic, with the first phase representing tissue injury and the second representing autoimmunity. Tissue injury (from immune or nonimmune insults) exposes normally sequestered self-antigens, and their fragments are released into the lung, acting as triggers for autoreactive T-cell proliferation and autoantibody production. The exposed self-antigens can thus sustain rejection even in the absence of persistent alloimmunity.[29]

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Type 5 collagen [col(V)], which resides beneath the basement membrane in the perivascular and peribronchiolar tissues of the lung,[30] was the first described potential self-antigen. A murine model of acute rejection demonstrated deposition of antibody in these regions, with col(V) being the recognized antigen.[31] Upon exposure to col(V) fragments, autoreactive T cells specific to col(V) proliferate and secrete cytokines consistent with a Th1 response.[29] Interestingly, induction of alloimmune injury to the lung allograft also potentiates the production of col(V) antibodies.[22] Translating this work into human subjects, Wilkes and colleagues[31] prospectively monitored responses to col(V) in lung transplantation recipients over a 7-year period using a novel trans vivo delayed-type hypersensitivity assay. The results were striking, noting a fivefold to 10-fold increased risk of high-grade BOS in those patients with elevated col(V)-specific cell-mediated immunity.[32] Further investigation suggested that autoreactive Th17 cells, known to be associated with chronic fibrotic autoimmune diseases in humans, in part mediate this response. In added support of this concept, a separate study found several cytokines important in Th17 cell development to be present in increased amounts in BAL fluid from patients with BOS compared with control subjects.[33] Recently, other novel autoimmune targets on the epithelial cell surface, including K-α1 tubulin, have been identified, and binding of autoantibodies to these targets has been shown to promote fibroproliferative events in vitro.[34]

The concept of inducible immune tolerance to col(V) or other self-antigens is highly intriguing, and exploitation of this idea may represent a future novel approach to the prevention or treatment of BOS. Rats fed col(V) prior to lung allograft transplantation were rendered tolerant to col(V) and, even in the absence of immunosuppression, did not develop acute or chronic rejection.[29] Regulatory T cells, tasked with maintaining immune homeostasis, are important in the development of immune tolerance. The function and regulation of autoimmune-inducing Th17 cells and tolerance-generating regulatory T cells are only now being examined in detail in solid organ transplantation. As an alternative to tolerance promotion and generation of regulatory T cells, strategies that target the effector Th17 pathway might also represent a viable therapeutic option in the future. For example, a humanized monoclonal antibody to interleukin-17A recently has been developed and found to be effective in the treatment of several autoimmune diseases.[35] Continuing to focus on autoimmunity could lead to the identification of novel targets for the treatment or prevention of BOS and revise our current thinking about transplantation immunosuppression.

Innate Immunity and Response to Environmental Insults

In recent years, the central importance of innate immunity in host defense has been recognized, particularly with the identification of toll-like receptors (TLRs) in humans. Innate immunity relies on recognition of highly conserved microbial pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by innate pattern recognition receptors (PRRs). TLRs, the prototypic family of innate PRRs, are found on pulmonary antigen-presenting cells and lung epithelium where they regulate the pulmonary response to inhaled toxins and infections. Both exogenous and endogenous ligands for these receptors have been described, including lipopolysaccharide (LPS), high-mobility group box 1, and hyaluronan fragments.[36] Signaling through TLRs promotes the development of acute inflammation; recruits and activates other antigen-presenting cells; and, more importantly, instructs and shapes the adaptive immune response.[36-38]

In the context of lung transplantation, genetic studies support the importance of innate immunity and TLRs in the pathobiology of BOS. Polymorphisms in both TLR4 and CD14, which binds LPS and promotes signaling through TLR4, have been shown to modulate the risk for BOS. Lung transplant recipients with loss-of-function TLR4 polymorphisms, in which the innate immune response to LPS is blunted, demonstrate significantly less acute rejection and a trend toward reduced high-grade BOS.[39] More convincingly, recipients with gain-of-function polymorphisms in CD14 develop BOS at earlier time points after transplantation and demonstrate increased BOS-related death compared with recipients with wild-type genotypes.[40] Murine studies validate the importance of innate immunity in mediating transplantation rejection. Exposure to aerosolized LPS in a mouse model has been shown to potentiate alloimmune lung disease with histologic features of lymphocytic bronchiolitis and chronic alloimmune lung injury.[41] Additionally, others have demonstrated that targeted deletions of MyD88 (an adaptor molecule shared by most TLRs) in mice can prevent skin allograft rejection.[42]

Taken together, these data suggest a constant interplay among environmental stimuli, the innate immune response, recipient genetic susceptibilities, and adaptive immunity. In fact, many of the previously identified and emerging clinical risk factors for BOS[7,43-46] are factors that would be likely to activate pulmonary innate immunity (Table 1). For example, release of endogenous DAMPs likely occurs with primary graft dysfunction after lung transplantation. In support of this idea, renal allograft ischemia

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Table 1—*Clinical BOS Risk Factors That Activate Pulmonary Innate Immunity*

Prolonged ischemic time	Primary graft dysfunction
Cytomegalovirus pneumonitis	Gastroesophageal reflux disease
Aspergillus colonization	Community respiratory virus infection

BOS = bronchiolitis obliterans syndrome.

reperfusion injury was recently shown to be mediated by the endogenous TLR4 ligand high-mobility group box 1.[47] Additionally, LPS, a predominant component of gastric refluxate, may drive pulmonary TLR activation and promote BOS in patients with gastroesophageal reflux disease. Respiratory syncytial virus, a common viral infection after lung transplantation that has been linked to a higher incidence of BOS, also has been shown to signal through the TLR pathway through the fusion protein moiety in its viral coat.[48]

Further identification of the specific PAMPs, DAMPs, and PRRs involved in the pulmonary allograft response to each of these clinical risk factors would offer the ability to selectively target and block pathways that upregulate the subsequent adaptive immune response. Therapies that target specific TLR or downstream signals currently are in development for sepsis and could translate to applications in lung transplantation. In addition, strategies aimed at reducing lung allograft PAMP and DAMP exposure, such as early Nissen fundoplication in recipients with gastroesphageal reflux disease, have shown promising results both in the prevention and in the treatment of BOS in small, single-center trials.[49,50]

Conclusions

BOS is the principal factor limiting long-term survival and quality of life after lung transplantation. Alloimmune reactivity plays a fundamental role in the development of BOS, and although T cells have been the traditional target of posttransplant immunosuppression, more potent T-cell-suppressing agents and innovative means of immunosuppressive drug delivery may further minimize the impact of the alloimmune response. Importantly, several exciting novel mechanisms, including antibody-mediated rejection, autoimmunity to col(V) and other self-antigens, and the activation of innate immunity in response to environmental and endogenous insults, have now been recognized to contribute to the fibroproliferative cascade of events leading to BO. Each of these newly identified immune mechanisms offers novel therapeutic or preventive targets (Fig 3) and ultimately offers the opportunity to individually tailor immunosuppressive therapies to a particular patient. For example, the identification of patients with DSA using flow-based serologic assays facilitates targeted augmentation of immunosuppression with IVIG, rituximab, or even bortezomib in select patients with a strong component of humoral reactivity. Clearly, further research into these and other mechanisms of lung rejection are necessary in order to establish a truly tailored approach to the prevention and treatment of BOS. Through such research, the burden of BO among lung allograft recipients can be reduced, enabling lung transplantation to become a more durable and effective long-term treatment of the ever-increasing number of patients with advanced lung disease.

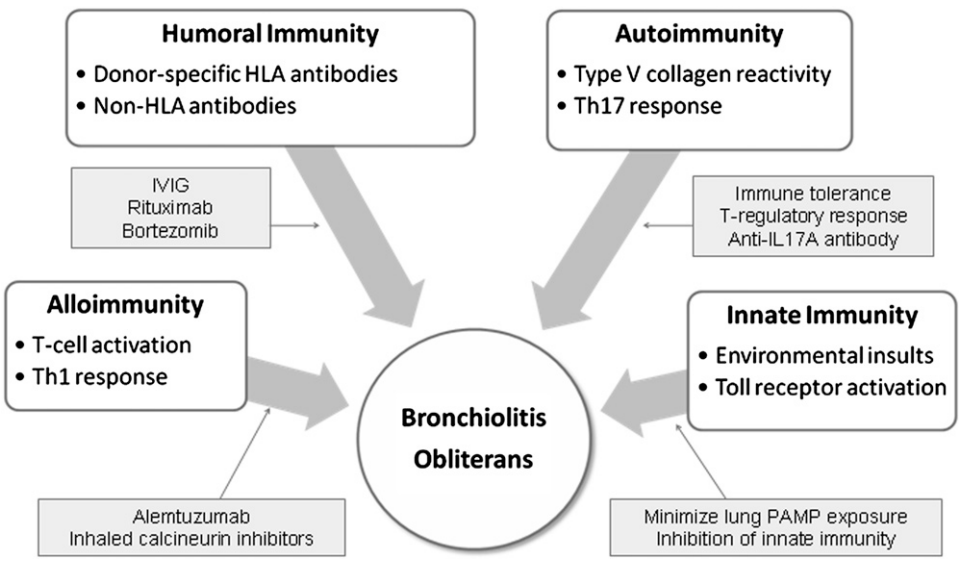

Figure 3. Multiple immune mechanisms contribute to the development of BO. Potential therapeutic targets are highlighted. HLA = human leukocyte antigen; IVIG = IV immunoglobulin; PAMP = pathogen-associated molecular pattern; Th = T helper. See Figure 1 legend for expansion of other abbreviation.

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