Bronchiolitis Obliterans Syndrome 2001: An Update of the Diagnostic Criteria

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Bronchiolitis obliterans (BO) is a major cause of allograft dysfunction in lung and heart lung transplant recipients.[1,2] Clinically, progressive airflow limitation develops because of small airway obstruction. The disease has a variable course. Some patients experience rapid loss of lung function and respiratory failure. Others experience either slow progression or intermittent loss of function with long plateaus during which pulmonary function is stable. Histologic confirmation is difficult because transbronchial biopsy specimens often are not sufficiently sensitive for diagnosis. Because BO is difficult to document histologically, in 1993 a committee sponsored by the International Society for Heart and Lung Transplantation (ISHLT) proposed a clinical description of BO, termed *bronchiolitis obliterans syndrome* (BOS) and defined by pulmonary function changes rather than histology. Although this system does not require histologic diagnosis, it does recognize it.[3]

Transplant centers worldwide have adopted the BOS system as a descriptor of lung allograft dysfunction. This allows centers to use a common language to compare program results. In the years since publication of the BOS system, transplant scientists have studied basic and clinical aspects of lung transplant BO. In this document, we update and summarize new information obtained from this research and incorporate, where appropriate, the results into the BOS criteria.

The document will include the following topics: (1) criteria for BOS, (2) BOS considerations in pediatric patients, (3) risk factors for BOS, (4) pathology of BO, (5) surrogate markers for BOS, (6) confounding factors in making a BOS diagnosis, and (7) assessment of response to treatment of BOS.

CRITERIA FOR BOS

Background

When the original definition of BOS was formulated in 1993, the working group had several goals. The group aimed to provide a classification system for airway disease after lung transplantation that did not rely on histopathologic findings, was sensitive and specific, relied on diagnostic techniques available to all lung transplant physicians, and was relatively simple to understand and apply. The resulting classification system defined post-transplant

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pulmonary function using the forced expiratory volume in 1 second (FEV_1) as the primary parameter. For each lung transplant recipient, a stable post-transplant baseline FEV_1 is defined as BOS Stage 0. In patients who experience a decrease in FEV_1, progressive stages of BOS, from 1 to 3, are defined according to the magnitude of the decrease. An additional notation can reflect histologic findings: "a" designates that no BO has been identified, or that no biopsy has been done; and "b" designates that BO has been identified.[3]

Although the ISHLT classification system for BOS has gained universal acceptance, several limitations have been identified. First, the current grading system—which defines BOS 1 as a >20% decrease in FEV_1 from baseline—was not sensitive enough to pick up early, small, but potentially important changes in pulmonary function.[4–6] In addition, the mid-expiratory flow rate ($FEF_{25–75}$) was not used for defining airflow obstruction because the wider intrasubject variability of this index, in particular in recipients of unilateral transplants,[7] and the very high values observed in some patients early after surgery were considered as potential limitations. Yet several reports in recipients of bilateral and heart–lung grafts have shown that $FEF_{25–75}$ is more sensitive than FEV_1 for early detection of airflow obstruction in BOS[4–6] (one study also included recipients of single lung transplants but results in these patients were not reported specifically[8]). These observations have led to a critical re-examination of the BOS criteria, and formulation of the revised classification system as detailed in this document.

Recommendations

1. Definition of BOS: We use the term *bronchiolitis obliterans syndrome* to connote graft deterioration secondary to persistent airflow obstruction (however, note that not all patients in whom airflow obstruction develops have BOS—see confounding conditions discussed below). It is widely presumed, but unproved, that chronic rejection often contributes to functional deterioration. BOS does not necessarily require histologic confirmation; in contrast, the term *bronchiolitis obliterans* is used for a histologically proven diagnosis.
2. Definition of equipment: Spirometric measurements must be made with equipment that conforms to the American Thoracic Society standards for spirometric testing.[9]
3. Definition of baseline: The *baseline value*, to which subsequent measures are referred, is defined as the average of the 2 highest (not necessarily consecutive) measurements obtained at least 3 weeks apart, such measurements being made without the use of an inhaled bronchodilator preceding the study. The *baseline date* is defined as the date of the first measurement used to compute the baseline. The values used to compute the baselines for FEV_1 and for $FEF_{25–75}$ may be obtained on different days. Because spirometric values may increase with post-operative time, the baseline should be recalculated using the highest values achieved. The definition of baseline, and hence of BOS stages, is expected to be more accurate as more functional tests are performed.
4. Definition of confounding conditions: Patients are evaluated under this system only after evaluation of other conditions that may alter graft function and after treatment of these conditions if found. Interpretation of changes in lung function should take into account confounding conditions, which are discussed below.
5. Definition of variables: In the original staging system, a ≥20% decrease in FEV_1 from previous baseline was used to diagnosis BOS. Studies of intrasubject variability of spirometry in lung transplant recipients indicate that using a 10% to 15% decrease in FEV_1 may be more appropriate for early detection of BOS.[5–7] In addition, evidence suggests that $FEF_{25–75}$ deteriorates before FEV_1 in most bilateral and heart–lung transplant recipients with BOS.[4–6] Therefore, a *potential-BOS stage* (BOS 0-p), defined by a 10% to 19% decrease in FEV_1 and/or by a ≥25% decrease in $FEF_{25–75}$ from baseline is added to the original staging system. This potential-BOS stage alerts the physician to the need for close functional monitoring and in-depth assessment, which might include surrogate markers for BOS (see below).
6. Definition of BOS stages: For the purpose of staging, a significant decrease in FEV_1 or $FEF_{25–75}$ will be determined by the average of 2 measurements made at least 3 weeks apart, without patient use of an inhaled bronchodilator. Patients having a single measurement of decreased FEV_1 or $FEF_{25–75}$ are not evaluated until a second measurement is obtained at least 3 weeks after the initial data point. Because BOS is meant to represent a persistent alteration in lung function, additional values of FEV_1 or $FEF_{25–75}$, which may be obtained during this 3-week period,

TABLE I Original and proposed classifications of BOS

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

BOS, bronchiolitis obliterans syndrome; FEF_{25-75}, mid-expiratory flow rate; FEV_1, forced expiratory volume in 1 second.

should also show a significant decrease from baseline value. The date at which a patient enters the new BOS stage is the date of the first of the 2 measurements used to confirm the stage. In case of a concomitant decrease in vital capacity (VC) and FEV_1, a restrictive ventilatory defect should be excluded before categorizing the patient in a new BOS stage (see confounding conditions discussed below).

7. Definition of functional decline: Because a universal table for converting the absolute value of FEV_1 and FEF_{25-75} to "percent predicted" does not exist, a fractional decrease in FEV_1 and FEF_{25-75} should be determined from absolute values. The fractional decrease in FEV_1 and FEF_{25-75} shall be expressed as the percent of decrease from the previously established baseline, i.e., the highest previous baseline value is used for all subsequent calculations.
8. Definition of staging system: A proposed staging system is outlined in Table I. Within each of the staging categories is an "a" and a "b" subcategory. These relate to histologic findings of biopsy specimens. This staging system is intended to describe the recipient's current status. Although BOS is considered irreversible, a minority of patients may show improvement in lung function over time. When a patient experiences such improvement in BOS stage, the worst stage that the patient has ever achieved may be noted in parentheses, if desired for study purposes. Therefore, BOS 1(2) will indicate a patient currently in BOS 1 who has been in BOS 2 at some point in the past.

BOS CONSIDERATIONS IN PEDIATRIC PATIENTS

Background

Approximately 2.5% of lung transplant candidates are ≤17 years of age. In terms of the number of transplants, number of patients on the waiting list, and number of active centers, pediatric lung transplantation lags behind adult lung transplantation and other pediatric solid-organ transplantation. Published reports indicate an incidence of BO similar to that of adults,[10–12] except in children <3 years old, in whom it may be lower.[10]

Airway inspection is particularly important in children to assess for stenosis and/or malacia at the anastomotic site. In general, the BOS criteria can be used in children who can perform pulmonary function tests reproducibly (usually at least 5 years of age). However, in defining functional decline, a decrease in percent predicted rather than a change in absolute value (see 7 above) should be used. The use of percent predicted values for FEV_1 and FEF_{25-75} should be a more accurate indicator in children because absolute values of lung function should increase with the child's growth. In older children who can perform reproducible respiratory maneuvers, the adult criteria with the use of predicted values should be easily applied. Because of the difficulty in performing pulmonary function studies in some pediatric patients, surrogate markers for BOS may assume more importance. Infants and young children require lung function testing by other techniques, most commonly through the rapid compression technique. The combined use of forced expiratory flow at functional residual capacity, normalized by the measured functional residual capacity, is a useful technique to separate anastomotic complications from peripheral airflow obstruction. Techniques for lung function testing in infants and young toddlers provide tools for performing serial lung function testing in lung transplant recipients of this age.[13,14] Experience with such techniques is limited to 1 pediatric lung transplant center,[15] and further clinical research with newer techniques is clearly indicated.

Recommendations

1. Pediatric patients suspected of having BO should undergo bronchoscopic examination of the airways and transbronchial biopsy when possible. On occasion in young patients or in those with obscuring clinical or large airway pathology, an open lung biopsy to assess for histopathology may facilitate early therapeutic intervention.
2. In general, the criteria for BOS can be applied in children who can complete pulmonary function tests satisfactorily. However, declines in function should be expressed in terms of percent predicted instead of absolute values because of lung and airway growth. Newer techniques facilitate measurements in infants and have been used to assess for BOS.

RISK FACTORS FOR BOS

Background

Many factors have been reported as risk factors for BOS. However, quality of data is often a problem because almost all existing information derives from retrospective studies with no control groups and reflects the experience of single centers. Numbers are small and often difficult to interpret. In some cases, risk factors seem to have been more important in the earlier years of lung transplantation, e.g., cytomegalovirus (CMV) infection. This may reflect a change in the risk environment because of the use of prophylactic antimicrobial regimens, changing immunosuppressive approaches, or the increasing experience of transplant management teams.

Alloimmunologic injury directed against endothelial and epithelial structures have been thought to mediate BOS, but non-alloimmunologic inflammatory conditions including viral infections or ischemic injury may also play a role. Risk factors reported in the literature will be designated as (1) probable risk factors, (2) potential risk factors in need of further analysis, and (3) hypothetic risk factors.

Probable Risk Factors

Acute rejection and lymphocytic bronchitis/bronchiolitis belong to this category. Six separate publications document the increased incidence of BOS in patients with acute rejection episodes, especially when multiple and/or long-lasting and/or high-grade episodes occur.[16–21] Two additional publications document the role of late acute rejection in the development of BOS.[22,23] Five publications report that lymphocytic bronchitis/bronchiolitis is a risk factor for BOS, when infection has been excluded as a cause of an inflammatory airway process.[18,20,24–26]

Medication non-compliance is a known risk factor for rejection and graft loss after kidney, heart, and liver transplantation.[27–30] Medication non-compliance also is perceived as a risk factor after lung transplantation, although results supporting this have not been published.

Cytomegalovirus is difficult to interpret as a risk factor for 2 main reasons: the pattern of CMV has changed with the widespread use of prophylactic strategies directed against the virus and with varying definitions of infection, disease, and pneumonitis among institutions. Eight reports consider CMV a risk factor for BOS,[16,19,22,25,31–34] whereas 4 other studies reported no impact of the virus.[18,20,21,35] Four other studies document a decreased risk of CMV in the development BOS—either decreased incidence or delay in onset—after the use of CMV prophylaxis.[17,36–38] However, data from the pre-prophylaxis era in which CMV pneumonitis was more prevalent strongly correlates pneumonitis as a BOS risk factor.

Potential Risk Factors

Potential risk factors are so designated because of conflicting data, suggestive but not definitive data, or differences in definitions of the specific risk factor between centers so that available data cannot be interpreted. These factors include (1) organizing pneumonia; (2) bacterial, fungal, and non-CMV viral infection; (3) older donor age; (4) longer graft ischemic time; and (5) donor antigen-specific reactivity.

Two centers report that organizing pneumonia is a risk factor for BOS. One of these centers reported that it was a univariate risk factor for BOS. The data are from small numbers and not complete enough to designate it a probable risk.[18,19]

A surprisingly small body of data has been published that report the impact of bacterial, fungal, and non-CMV viral infections. One center reported bacterial and P carinii pneumonia as risks during the period before broad-spectrum prophylaxis in lung transplantation.[17] In a more recent report, bacterial or fungal pneumonia was not associated as an univariate risk with an increased rate of BOS, but did increase the acute rejection score in a multivariate model.[18] A peak incidence of BOS onset in the respiratory virus season suggested to one set of authors that common respiratory viral infections may trigger the complication.[39] Treatment of respi-

ratory syncytial and parainfluenza viruses decreased the incidence of BOS in one center.[40]

Donor age did not correlate with BOS in a large population in the United Kingdom; however, the ISHLT 2000 Registry identified donor age as a risk factor.[19,41] The Registry identified graft ischemic time as a second donor risk factor, a finding also differing from the findings of the UK study.

Persistent donor antigen-specific reactivity has reportedly led to increased rates of BOS, and conversely, donor-specific hyporeactivity was reported as protective.[42,43] Preliminary experience from the Pittsburgh Transplant Group has shown that the infusion of donor bone marrow in combination with lung transplantation increases donor cell chimerism and donor antigen-specific hyporeactivity, and is associated with a lower incidence of BOS.[44]

Hypothetic Risk Factors

Hypothetic risk factors include factors supported by theoretical considerations but having scanty clinical evidence to date. These factors include (1) underlying disease, (2) genotype of the recipient for certain cytokine gene polymorphisms, (3) HLA-mismatching, and (4) gastroesophageal reflux with aspiration.

Two studies suggested that underlying diagnosis is a risk factor and that patients with pulmonary hypertension may be more at risk of BOS; in a third study, this was not the case.[17,25,33] The ISHLT 2000 Registry identifies emphysema patients as having the best survivals but does not identify freedom from BOS as the reason.[41]

Data are emerging on the potential role for genotypic susceptibility to development of BOS. Cytokine gene polymorphisms of tumor necrosis factor (TNF)–α, interferon γ, IL-10, IL-6, or TGF-β genes may play a role.[45] Available data are scant and conflicting.[46]

Data also conflict on HLA mismatching, with most series showing no association.[17,18,20] One institution has documented an increased risk of BOS with the development of anti-HLA Class I antibodies.[47] Confusion in this area arises in part from the small number of transplantations performed in individual centers and because no attempt at HLA matching is made. Therefore, it is uncommon for any center to have more than a few HLA-matched recipients. In the largest study yet reported that involves HLA matching, 3,549 lung transplantations were reviewed using the United Network for Organ Sharing (UNOS)/ISHLT Registry database. Only 164 patients had 2 or fewer mismatches. No significant association could be found between HLA mismatching and BOS development.[48]

TABLE II Risk factors for BOS

Probable risk factors:
Acute rejection
Lymphocytic bronchitis/bronchiolitis
CMV pneumonitis
Medication non-compliance
Potential risk factors:
CMV infection (without pneumonitis)
Organizing pneumonia
Bacterial/fungal/non-CMV viral infection
Older donor age
Longer graft ischemic time
Donor antigen-specific reactivity
Hypothetic risk factors
Underlying disease
HLA-mismatching
Genotype of recipient
Gastroesophageal reflux with aspiration

BOS, bronchiolitis obliterans syndrome; CMV, cytomegalovirus.

Case reports and small series have suggested an incremental risk from gastroesophageal reflux disease with aspiration and from impaired mucociliary clearance.[49–52]

Several additional factors, including history of smoking or asthma in the donor, head injury as cause of death, airway ischemia, and diffuse alveolar damage (reperfusion injury), have been proposed as risk factors for late organ dysfunction. However, convincing data to support the role of these factors are lacking.[20,53–56]

A differential in the prevalence of BOS among unilateral, bilateral, and heart–lung grafts has not been documented.

Recommendations

1. Many factors have been reported as potential risk factors for BOS, but proven causal relationships are difficult to establish.
2. Based on available information, Table II summarizes the probable, potential, and hypothetic risk factors.

PATHOLOGY OF BO

Background

Bronchiolitis obliterans is a cicatricial process that affects the small airways of the allograft lung. Conceptually, BO is thought to result from chronic lung rejection, although not exclusively. It progresses through a sequence of lymphohistiocytic-mediated

cytotoxicity directed at the respiratory epithelium. The initial process is a lymphocytic infiltrate of the sub-mucosa of the airways with migration of lymphocytes through the basement membrane into the epithelium.[57] At this site, epithelial cell necrosis occurs with denudation of mucosa. A secondary cascade of non-specific inflammatory mediators and cytokines attracts other cells, including neutrophils. The reaction stimulates migration of fibroblasts and myofibroblasts into the luminal exudate. Formation of an intraluminal fibromyxoid granulation tissue polyp results. In some instances, macrophage collagenases may dissolve the polyp. The diagnostic fibrous scarring can be eccentric with formation of a fibrous plaque in the wall of the airway; concentric with the interposition of a "donut" of collagen tissue; or the granulation tissue may completely obliterate the lumen of the airway, reducing the air passages to stenotic cords of scar tissue ("vanishing airways disease").[58] At the time of histologic diagnosis, the airway injury may be temporally heterogeneous with some airways showing only cellular infiltrates, some displaying active fibroplasia, and others demonstrating inactive fibrosis.

Bronchoscopy may exclude other causes of deteriorating lung function, but diagnosing BO with transbronchial biopsy specimens may be extremely difficult. It requires multiple, large fragments, and even then, diagnostic lesions may be missed. Trichrome and elastic tissue stains may assist in recognizing the damaged or obliterated airway. When the clinical diagnosis is unclear and transbronchial biopsy specimens have not offered an unequivocal answer, open lung biopsy may be necessary.

The initial document describing BOS used an "a" sub-category to designate no pathologic evidence of BO (or no pathologic material for evaluation) and a "b" sub-category to mean that pathologic evidence of BO was obtained. The usefulness of these designations has not yet been validated.

Recommendations

1. Histologic activity may not reflect the clinical activity monitored by pulmonary function tests.
2. The term *bronchiolitis obliterans* should be used only when histology demonstrates dense fibrous scar tissue affecting the small airways.
3. The presence of only lymphocytic sub-mucosal infiltrate or intraluminal granulation tissue is not sufficient for a diagnosis of BO.
4. If the obliterative lesion is associated with a mononuclear infiltrate, it is defined as active; fibrosis without inflammatory cells is defined as inactive.
5. An "a" sub-category designates no pathologic evidence of BO (or no pathologic material for evaluation). A "b" sub-category means that pathologic evidence of BO has been obtained.

SURROGATE MARKERS FOR BOS

Background

The diagnostic criteria for BOS are based on a decrease in lung function. Various indirect measures or analyses have been undertaken to identify alternative early markers of a decrease in graft performance. Perhaps these markers can provide a surrogate means of predicting disease or of monitoring disease activity, with the aim of enabling early therapy to block a relentless decrease in lung function.

Bronchoalveolar lavage (BAL) analysis

A number of cross-sectional studies[59–64] and 3 prospective studies[7,60,64] indicate an association between BOS and BAL neutrophilia, and they indicate that this alteration may actually precede the 20% decrease in FEV_1 required for the spirometric diagnosis of BOS.[7,60,64] In addition, a persistent increase in BAL neutrophilia is an independent predictor of mortality after lung transplantation.[65] Other preliminary studies implicate various BAL markers or mediators in the pathogenesis of BOS (e.g., IL-8, markers of oxidative stress, neutrophil elastase, TGF-β, platelet derived growth factor (PDGF), collagen I/III, insulinlike growth factor-1). Although these markers may provide useful concepts for exploring the mechanisms behind development of chronic allograft rejection, they are not yet sufficiently robust tests to contribute to the clinical diagnosis of BOS.

Exhaled nitric oxide

Exhaled nitric oxide (eNO) provides a potentially useful tool in diagnosing acute and chronic allograft rejection in lung transplant recipients. Several lung transplant centers have evaluated eNO and found it to be reproducible, repeatable, and reflective of NO levels in the lower airways.[66,67] The source of eNO in allograft pathology remains to be identified, but potential sources include epithelial cells and infiltrating leukocytes;[67–69] eNO has a close link with BAL neutrophilia.[67] A cross-sectional study of 104 lung transplant recipients noted elevated eNO in

lymphocytic bronchitis and BOS Stage 1 but not in BOS Stages 2 and 3.[70] Other studies have reported a variable association between increased eNO and BOS.[71,72]

Air trapping shown on expiratory computerized tomography scans

Imaging is a potentially simple and repeatable means of assessing BOS. High-resolution computerized tomography (CT) scanning is the most accurate imaging tool for diagnosing BOS. On inspiratory scans, several abnormalities have been associated with BOS, including bronchial dilatation, bronchial wall thickening, and mosaic perfusion pattern, although these findings lack sensitivity.[73–76] In contrast, the presence of air trapping on expiratory CT scans is an accurate indicator of the bronchiolar obliteration underlying BOS.[77–80] In patients with BOS, the pulmonary lobules that have normal airways increase in density during the expiratory phase, whereas areas with diseased airways cannot empty and remain radiolucent secondary to the obstructive bronchiolar inflammatory and fibrotic changes. In a recent prospective study that included 111 expiratory CT scans in 38 heart–lung transplant recipients, the presence of air trapping >32% had a 87.5% sensitivity and specificity for the diagnosis of BOS, and in some patients this preceded the spirometric criteria for BOS.[79] Conversely, having <32% of air trapping had a high negative predictive value until the fifth post-operative year. In another, smaller study, an air-trapping score provided a sensitivity of 74% and a specificity of 67% for histopathologically proven OB.[80]

Bronchial hyper-responsiveness.

Bronchial hyper-responsiveness has been reported in patients who have undergone lung transplantation, although some studies have been negative for this finding.[81–89] In a recent longitudinal study that included 111 patients undergoing bilateral lung transplantation, Stanbrook and Kesten[89] reported that 30% of patients had a positive methacholine challenge at 3 months after transplant and were significantly more likely to have BOS; the mean time to development of BOS was 16.9 months. A retrospective study of 94 lung transplant recipients showed that the presence of a bronchodilator response at low lung volume had a sensitivity of 51%, a specificity of 87%, and a positive predictive value of 81% for the diagnosis of BOS.[90] This study also noted that the bronchodilator response may precede BOS by months.

Distribution of ventilation.

Two recent prospective studies have shown that indices of ventilation distribution (e.g., the alveolar plateau slope obtained for nitrogen or helium during single-breath washout) may detect BOS earlier than do conventional pulmonary function tests.[6,7] Reynaud-Gaubert et al[6] considered a nitrogen slope >3% as abnormal, whereas Estenne et al[6] considered significant a 100% increase above baseline.

Problems with and quality of data.

In addition to the limitations that clinical trials in lung transplant recipients frequently encounter (small sample size, retrospective study, lack of adequate control group), 3 specific limitations should be mentioned in the context of the surrogate markers for BOS:

1. Many of the markers discussed above have been used and validated primarily in recipients of heart–lung and double-lung grafts, e.g., air trapping on expiratory CT and indices of ventilation distribution. No clear effect on eNO caused by the type of surgical procedure or the type of disease in the native lung has been demonstrated in transplant recipients who are stable or who have BOS. This point deserves further study.
2. Specificity of the markers discussed here for the diagnosis of BOS is low, e.g., BAL neutrophilia may be caused by infection, and eNO or indices of ventilation distribution may increase in acute rejection or infection.
3. Thresholds indicating a significant alteration from the stable state, particularly for BAL neutrophilia and eNO, have not been clearly established. These thresholds must be determined on the basis of standardized baseline values[91] using intrasubject coefficients of variation.

Recommendations

1. BAL neutrophilia and elevated cytokine levels, eNO, air trapping on expiratory CT scans, bronchial hyper-responsiveness, and measures of an altered distribution of ventilation have all been identified as early markers of BOS. However, none is specific or sensitive enough to be used reliably for diagnosing BOS.
2. The presence of an abnormal level of a surrogate marker should alert the clinician to the potential for BOS onset.

CONFOUNDING FACTORS IN DIAGNOSING BOS

Background

Lung function is exquisitely sensitive to complications that affect the allograft, such as rejection, infection, and anastomotic complications. These complications often produce some degree of airflow obstruction and may lead to a pattern of functional deterioration, which is qualitatively similar to that seen in BOS. In addition, several complications that affect the native lung and disease progression in the native lung may contribute to changing pulmonary function. This section addresses (1) confounding factors in the graft that apply to all types of transplants, (2) confounding factors that affect the native lung in single lung transplants, and (3) confounding factors that cause a restrictive ventilator defect.

Factors that affect the graft.

- Infection and rejection: Symptoms characteristic of infection frequently herald the onset of BOS, and a community-acquired respiratory bacterial or viral infection may be documented. Similarly, some patients with recurrent or refractory acute rejection (including acute cellular rejection and lymphocytic bronchitis/bronchiolitis) progress to BOS. Therefore, the presence of infection or acute rejection, which may produce airflow obstruction,[92] does not exclude the diagnosis of BOS and may confound its early diagnosis. If the lung function change persists after appropriate treatment, the diagnosis of BOS can be made.
- Anastomotic complications: Complications at the site of the tracheal or bronchial anastomosis (e.g., stenosis, dehiscence, and malacia) may alter forced expiratory flows and volumes. Because these complications occur early after surgery, they are generally recognized before the diagnosis of BOS is suspected. Yet interpretation of functional changes in the presence of anastomotic complications may be difficult because it is not always easy to determine whether stenosis/malacia or the development of BOS is responsible for a decrease in lung function. The final diagnosis is left to the discretion of the individual physician.
- Disease recurrence: Some primary diagnoses have recurred in the lung graft. These include sarcoidosis, lymphangioleiomyomatosis, Langerhans cell histiocytosis X, alveolar cell carcinoma, desquamative interstitial pneumonitis, panbronchiolitis, and giant cell interstitial pneumonitis.[93–99] Disease recurrence may cause graft dysfunction, may confuse the diagnosis of BOS, or may coexist with BOS. In other cases, e.g., sarcoid, recurrent disease may have little functional effect. In the context of recurrent disease, the diagnosis of BOS must be made with caution unless histologic confirmation is available.
- Aging: In long-term survivors, the physiologic aging process of the lung is expected to significantly decrease both FEV_1 and $FEF_{25–75}$. However, making firm recommendations as to how to account for this factor is not possible because the rate of functional decline with age in an otherwise normal graft remains unknown.

Factors affecting the native lung.

- Native lung hyperinflation: Acute native lung hyperinflation is a complication reported in patients with emphysema who receive single lung transplants.[100–104] If acute native lung hyperinflation occurs early after surgery, it does not interfere with the diagnosis of BOS. However, intermediate- and long-term, progressive hyperinflation of the emphysematous lung may be associated with graft dysfunction.[105] Studies in stable recipients of single lung transplants for emphysema have shown that the total lung capacity of the graft is decreased to 66% to 79% of the predicted normal values.[106,107] In a small sub-set of patients, hyperinflation of the native lung may worsen over time and lead to clinical and functional changes similar to those produced by BOS (e.g., dyspnea, worsening airways obstruction, hypoxemia, accentuated radiologic shift of the mediastinum toward the graft, and V/Q mismatch). In this context, lung volume reduction or lobectomy of the native lung may improve lung function in selected individuals.[108–112] The mechanisms underlying delayed native lung hyperinflation have not been precisely identified, and more importantly, no easy means exist to distinguish between this complication and BOS. Moy et al[113] suggested that measuring lung resistance during inspiration may be helpful in this context, but further studies must validate the use of this variable. From a practical standpoint, if a patient with emphysema who has undergone single lung transplantation has worsening airflow obstruction without another specific cause, the patient should be considered to have BOS.
- Disease progression in patients without emphysema: Disease progression in the native lung may contribute partially to a change in overall lung function. However, because the native lung usually makes only a minor contribution to maximal expiratory flows and volumes, disease progression

is not expected to be a frequent confounding factor for the diagnosis of BOS.

- Other complications: Several complications may occur in the native lung and affect approximately 25% to 40% of the recipients.[114–117] Infectious complications are more frequent, and recipients who have emphysema seem to be at increased risk. However, complications affecting the native lung are easy to identify and generally do not interfere with the diagnosis of BOS.

Factors causing a restrictive ventilatory defect

Several diseases may decrease static and dynamic lung volumes in recipients of lung transplants. These conditions include increased body mass index,[118] respiratory muscle weakness unrelated[119] or related to generalized neuromuscular disorders, pleural effusion, rib fractures, chronic post-operative pain, and pulmonary edema. The functional impact is expected to be a decrease in both VC and FEV_1. Therefore, in the presence of a decreased FEV_1, an unchanged FEV_1/VC ratio should alert the clinician to exclude the above-mentioned conditions before considering the diagnosis of BOS. In the presence of a concomitant decline in VC and FEV_1 with an unchanged FEV_1/VC ratio, the baseline for FEV_1 and for $FEF_{25–75}$ may be reset to a lower value.

Recommendations

1. Infection, acute rejection, disease recurrence, and anastomotic complications can confound the diagnosis of BOS. These diagnoses should be excluded or treated before assigning a designation of BOS.
2. Following single lung transplant for emphysema, native lung hyperinflation occasionally results in a functional and physiologic picture similar to BOS. In this setting, a precise diagnosis may be impossible and each case should be judged on its individual characteristics.
3. A number of conditions can occur that cause decreases in both the VC and the FEV_1 (e.g., an increase in body mass index, muscular weakness, pleural effusion, etc.) without a decrease in the FEV_1/VC ratio. Such comorbidities must be excluded before assigning a diagnosis of BOS.

ASSESSING BOS RESPONSE TO THERAPY

Background

Although the fibrous obliteration of the bronchioles seen in BO probably is irreversible, the histologic lesions are often heterogeneous, with some airways showing inflammatory infiltrates potentially amenable to treatment. This probably explains why some patients show functional stabilization or improvement with treatment. Assessing response to therapy is difficult in individual patients because of the high variability of the disease response of an individual to an intervention.[9,120–125] This document proposes methods of assessing populations and study purposes. Retrospective and non-randomized designs, small sample size, absence of a control group, and relatively short follow-up have weakened published studies of treatment for BOS. Given the variable natural course of BOS, an appropriate number of patients in randomized studies with both a treated and a control arm is mandatory, and the method used to assess the response to therapy must be standardized. Designing multicenter studies with a large number of patients may allow stratification according to several factors that may affect response to therapy, e.g., BOS stage, association with acute rejection or lymphocytic bronchiolitis, rate of functional decrease, association with infection, time from transplantation to development of BOS, etc.

Recommendations

1. Assessing response to therapy should be based on the diagnostic criteria for BOS, i.e., FEV_1. Absolute values of FEV_1 measured before and after the therapeutic intervention should be plotted over time, and the slopes should be obtained by linear regression analysis. At least 3 measurements with a negative slope, obtained over 1 to 3 months, should be used to compute the slope before treatment. This slope should be calculated using all the data points obtained in the 1 to 3 months before initiation of treatment; the first point used should be the first measurement below the BOS threshold. The slopes after treatment should include all data points obtained after initiation of treatment and for at least a period of 6 months (see Appendix). A decrease in the rate of functional decline after initiation of treatment may be coincidental (i.e., reflect the natural history of the disease) and may not reflect a therapeutic benefit. This underscores the difficulty in interpreting the response in individual patients and emphasizes the need for control groups in prospective studies.
2. Stability may occur spontaneously after onset of BOS. This results in a flat FEV_1 slope (instead of a negative slope), and assessment of therapeutic intervention is problematic. Because this course of the disease occurs relatively frequently, pro-

spective studies assessing intervention probably will require large numbers of patients and prolonged study periods.
3. Comparisons of frequency of occurrence and progression through BOS grades are appropriate end-points for assessing therapy. In individuals, improvement in BOS grade is not expected or consistent with the current understanding of this syndrome.

FUTURE STUDIES

The committee recognizes that although BOS is the most common complication leading to chronic graft dysfunction and death of lung transplant recipients, it remains poorly understood. However, the course of disease progression may be quite variable for individual patients, suggesting a heterogeneous pathogenesis. Although lung function may decrease rapidly, leading to respiratory failure and death in some patients, other patients may survive for years with either stable or slowly progressive loss of lung function. Therefore, we recommend use of this document to stimulate collection of data and to underlie prospective studies that will lead to better understanding of and eventually prevention of this devastating complication. We suggest the following research priorities.

Risk Factors

1. Collation of existing large data bases to better define risk factors
2. Collaborative prospective collection of data in a centralized database to subsequently correlate with development of BOS

Criteria for BOS

1. Prospective collaborative studies to validate the usefulness of the new BOS 0-p stage, in particular in recipients of single lung transplants.
2. Prospective collaborative studies to evaluate survival and quality of life after BOS onset at each stage.
3. Prospective collaborative studies to define different courses of disease progression, risk factors for disease progression, and time of onset.
4. Prospective collaborative studies to evaluate the relative impact on survival, quality of life, and exercise capacity in double vs single lung transplant recipients.

Surrogate Markers

1. Prospective collaborative studies comparing surrogate markers with lung function and ability to predict future decreases in lung function.
2. Prospective collaborative studies to establish normative data and thresholds for significant change in markers such as BAL neutrophilia and eNO; prospective collaborative studies correlating changes in different surrogate markers.

APPENDIX

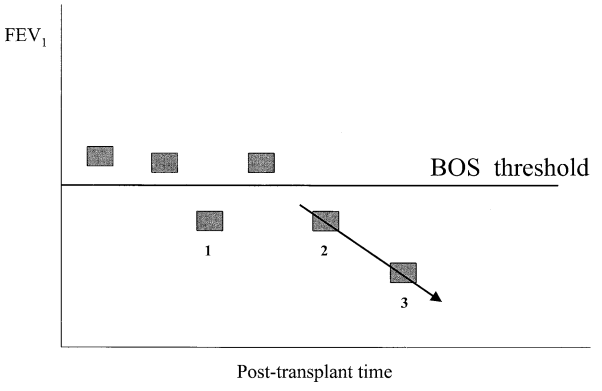

FIGURE 1 Event 1: drop below BOS threshold, not validated by second measurement. Event 2: first BOS measurement and time of onset of BOS defined by validating event #3. FEV_1 decline = slope of values 2 and 3 and any additional measurement over a 1–3 month period.

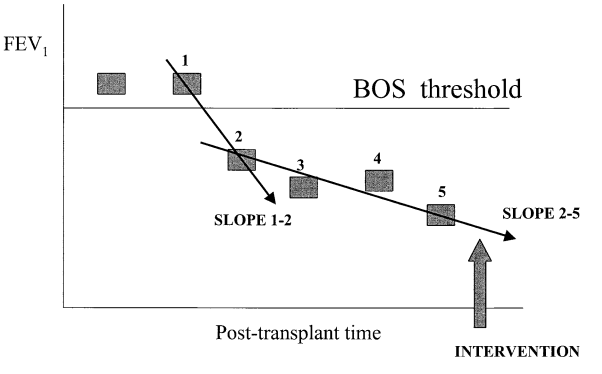

FIGURE 2 Though initial decline below BOS threshold shows a steep decline (slope 1–2), preintervention value 2 which defines BOS onset (and is validated by subsequent values) and subsequent values 3–5 define the slope prior to intervention. Benefit of therapeutic intervention will be defined by comparison with the slope 2–5.

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