Chapter 1
Bronchiolitis Obliterans Syndrome and Chronic Lung Allograft Dysfunction: Evolving Concepts and Nomenclature

Keith C. Meyer and Allan R. Glanville

Abstract Bronchiolitis obliterans syndrome (BOS) eventually occurs in the majority of lung transplant recipients who survive beyond 1 year, can greatly impair quality of life, and is, directly or indirectly, the major cause of delayed allograft dysfunction and recipient death. A number of associated events or conditions are strongly associated with the risk for developing BOS; these include acute rejection, gastroesophageal reflux, infections, and autoimmune reactions that can occur in the setting of alloimmune responses to the lung allograft as recipients are given intense immunosuppression to prevent allograft rejection. The term chronic lung allograft dysfunction (CLAD) is being increasingly used to refer to recipients with late allograft dysfunction that meets the spirometric criteria for the diagnosis of BOS, but clinicians should recognize that such dysfunction can occur for a variety of reasons other than BOS. The recently identified entity of restrictive allograft syndrome, which is now recognized as a relatively distinct phenotype of CLAD, has features that differentiate it from classic obstructive BOS. A number of other entities that can also significantly affect allograft function must also be considered when significant allograft dysfunction is encountered following lung transplantation.

Keywords Lung transplantation • Bronchiolitis obliterans syndrome • Obliterative bronchiolitis • Lung allograft rejection • Chronic lung allograft dysfunction • Restrictive allograft syndrome • Neutrophilic reversible allograft dysfunction

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Introduction

Late lung allograft dysfunction with progressive loss of function and graft loss was originally described for heart–lung transplant recipients in 1984 [1]. Histopathological postmortem examination of these lungs revealed lesions of constrictive bronchiolitis with airway fibrosis and luminal obliteration that was designated as obliterative bronchiolitis (OB). Late decline in allograft function following recovery and stabilization of lung function after the initial lung implantation was increasingly encountered as more lung transplants were performed in the late 1980s, and the consensus document that suggested that the term bronchiolitis obliterans syndrome (BOS) could be used to designate the syndrome of persistent loss of function with decline in FEV_1 that could not be explained by other, potentially reversible complications such as acute rejection or infection was published in 1993 [2].

Clinical experience that evolved over the subsequent 2 decades of lung transplantation has confirmed that the pathologic finding that usually correlates with a persistent decline in post-transplant FEV_1 that is consistent with the clinical diagnosis of BOS is the presence of the lesion of OB. The threshold of a ≥20 % decline in FEV_1 (with a pattern of airflow obstruction) from an established baseline was chosen in previous consensus documents [2, 3] as an appropriate surrogate marker of OB due to the strong association of OB with late chronic allograft dysfunction. Major considerations that led to choosing FEV_1 as a surrogate marker were (1) the relative difficulty of obtaining adequate diagnostic tissue via transbronchial lung biopsy (TBLB) plus (2) the desire to avoid the substantially increased risks of performing more invasive diagnostic procedures (i.e., surgical lung biopsy), although more extensive sampling of lung tissue could facilitate a more confident diagnosis (and may be considered necessary in certain situations). This chapter will provide an overview of current concepts pertaining to BOS and the terminology used to describe delayed or chronic allograft dysfunction.

An Overview of BOS Pathogenesis and Associated Risk Factors

Post-transplant OB is characterized by progressive obliteration of small airways accompanied by a persistent decline in FEV_1, an obstructive spirometric pattern, an essentially clear chest radiograph, and the lack of an alternative diagnosis to explain a persistent decline in lung function [2]. This syndrome was presumed to be caused by chronic allograft rejection, and the term chronic lung allograft dysfunction (CLAD) was coined and used to refer to allograft dysfunction that met the criteria that were adopted to indicate a diagnosis of BOS. Previously published consensus statements have designated a persistent decline in FEV_1 to ≤80 % of baseline post-transplant FEV_1 (that is present for a minimum of 3 weeks in the absence of confounding conditions) as a surrogate marker of probable OB (Table 1.1), and a staging system was devised to qualify the level of FEV_1 decline, which correlates fairly well with severity of allograft dysfunction.

Table 1.1 Diagnosis and grading of bronchiolitis obliterans syndrome

	Spirometry (% of baseline)	
BOS grade	1993 Classification	2002 Classification
0	FEV_1 ≥80 % of baseline	FEV_1 >90 % of baseline and $FEF_{25–75}$ >75 % of baseline
0p	Not applicable	FEV_1 81–90 % of baseline and/or $FEF_{25–75}$ ≤75 % of baseline
1	FEV_1 66–80 % of baseline	FEV_1 66–80 % of baseline
2	FEV_1 51–65 % of baseline	FEV_1 51–65 % of baseline
3	FEV_1 ≤50 % of baseline	FEV_1 ≤50 % of baseline

By definition, 3 or more months were required to have elapsed from the time of transplantation in order for the diagnosis of BOS to be made [2, 3]. This qualification was made to help distinguish BOS from non-BOS acute and/or subacute complications of lung transplantation as well as to take into account the time needed to establish both a baseline FEV_1 and a confirmed decline in FEV_1 with FEV_1 measurements taken 3 weeks apart. Because of concern that the cutoff value for FEV_1 at 80 % of the best post-transplant value may be insensitive to early decline in allograft function due to early OB, stage BOS-0p (FEV_1 = 81–90 % of baseline and/or $FEF_{25–75}$ ≤ 75 % of baseline) was added to the staging system to signify "potential BOS" [3]. One problem with this scheme is the considerable variation in FEV_1 values that some recipients may have due to the timing and fluctuation in spirometric measurements caused by various post-transplant complications that can prevent a recipient from achieving a graft function plateau with reasonably stable post-transplant FEV_1 values that accurately represent the zenith of attainable function. Such fluctuation and the consequent inability to establish stable post-transplant lung function make it difficult, if not impossible, to identify an accurate baseline value. The identification of other surrogate markers (e.g., biomarkers) that accurately reflect pathological airway and/or parenchymal processes for which specific interventions should be considered is much needed.

A considerable number of risk factors have been associated with the development of BOS (Table 1.2). BOS is widely perceived as the physiological surrogate of an immunologically mediated phenomenon due to many observations that include its association with acute cellular rejection [4], the association with greater degrees of HLA mismatch with BOS risk [5], and evolving evidence of the involvement of autoimmune pathways [6] and the interplay of alloimmune and autoimmune processes that can lead to allograft rejection [7]. Furthermore, lung histopathology in patients with BOS shows striking similarities to the OB that can occur in allogeneic bone marrow or stem cell transplant recipients as well as constrictive bronchiolitis in patients with connective tissue diseases [8–10], and these airway changes are perceived as alloimmune or autoimmune disorders, respectively. Nonetheless,

Table 1.2 Risk factors associated with BOS

Alloimmune rejection events
• Acute cellular rejection
• Lymphocytic bronchiolitis
• Humoral rejection (e.g., anti-HLA antibodies)
Acute allograft injury
• Primary graft dysfunction[a]
Autoimmune sensitization to self-antigens
• Collagen V
• κ (kappa)-α (alpha) 1 tubulin
"Non-immune"[a]
• Persistent BAL neutrophilia
• Gastroesophageal reflux and [micro]aspiration
▪ Acid reflux
▪ Nonacid reflux
• Infection or colonization
▪ Virus
• Cytomegalovirus
• Non-CMV community-acquired virus infection
▪ Bacterial (e.g., *Pseudomonas*)
▪ Fungal (e.g., *Aspergillus*)
▪ Air pollution
Other (putative) risks
• Ischemic airway injury due to disrupted bronchial microcirculation
• Accelerated allograft aging due to cell/tissue senescence
• Inadequate recipient compliance with outpatient drug therapies

BAL bronchoalveolar lavage, *CMV* cytomegalovirus, *HLA* human leukocyte antigen
[a]These likely involve allograft injury combined with triggering of innate immune responses that may also trigger or potentiate alloimmune/adaptive immune responses

although BOS is frequently equated with the term chronic rejection, various interventions, including intensified immunosuppression, may have little or no effect on the progressive loss of allograft function that is usually observed in lung transplant recipients who develop BOS. However, some patients can have significant clinical responses to alternative immunomodulatory therapies such as total lymphoid irradiation [11], or extracorporeal photopheresis [12], although these responses generally consist of stabilization or a decrease in the tempo of lung function loss over time and are unlikely to improve lung function (see Chap. 16).

In addition to alloimmune and/or autoimmune phenomena associated with BOS, various "non-immune" mechanisms have been implicated as playing a role in BOS pathogenesis. Although often referred to as nonimmune, these events/phenomena likely trigger or potentiate innate immune responses, which may also trigger or intensify alloimmune or autoimmune responses. These mechanisms include injury caused by primary graft dysfunction (PGD), gastroesophageal reflux (GER), and infections caused by viruses, bacteria, or fungi [13–15].

PGD, which affects 10–25 % of all lung transplants and is a leading cause of early morbidity and mortality, represents a form of acute lung injury that is considered to occur largely as a consequence of the periods of ischemia and reperfusion as the donor lung is procured and then implanted in the recipient [16–19]. Although a number of studies have not consistently linked PGD to BOS [20–24], more recent studies support a link between PGD and the development of BOS [25–27]. Daud et al. [25] found a convincing association of PGD grade with increased risk of developing BOS Stage 1 using International Society for Heart and Lung Transplantation (ISHLT) consensus definitions for PGD, and a more recent analysis of outcomes by this group identified a direct relationship between PGD severity at 24, 48, and 72 h post-transplant and increased risk of BOS [28]. The most severe grade of PGD (grade 3) at all three time points was associated with the highest risk of developing BOS (RR was 3.31 for grade 3 PGD at 24 h).

The presence of significant GER (GER that is increased in frequency/severity over what is considered normal) increases the risk that refluxate can be aspirated into the lower respiratory tract and has been linked to both subacute and chronic lung allograft dysfunction [29–36]. Multiple studies have reported a high prevalence of an abnormal degree of GER among patients with advanced lung disease and patients referred for lung transplantation [37, 38]. Approximately 70 % of patients who undergo transplant evaluation have some evidence of significant GER [38], and acid reflux may worsen following transplantation [39]. Gastroparesis and/or esophageal dysmotility may also be present and increase the risk of reflux and microaspiration. A negative correlation was found between increasing severity of acid reflux (as measured by 24-h pH study) and post-transplant FEV_1 [36], and the presence of nonacid reflux (as measured by impedance testing) was reported to increase the risk for BOS nearly threefold [33]. Refluxed bile acids in BAL fluid have been found to be increased in cross-sectional studies of patients with BOS [40, 41], and GER associated with aspiration of bile acids (bile acids detected in BAL) has been linked to BOS [40], a significantly increased risk of BOS onset [41], and poor response to azithromycin therapy [42]. Recent studies in animal models of lung transplantation suggest that gastric aspiration might enhance allorecognition and promote lung allograft rejection [43, 44], and GER has been linked to collagen V sensitization and BOS in transplant recipients [45].

Infections caused by viruses, bacteria, and fungi have been linked to risk for developing BOS (see Chap. 11). A large number of studies have linked pulmonary CMV infection to the subsequent development of BOS and/or diminished post-transplant survival [46–52]. Prophylactic and preemptive strategies to prevent/treat CMV infection have significantly reduced the incidence of CMV disease in lung transplant recipients [53–56], and retrospective studies of perioperative ganciclovir prophylaxis suggest that preventing CMV disease may delay the onset of BOS [57–59]. However, a recently published prospective, single-center study reported an incidence of CMV pneumonitis of 21 % within 6 months of transplant (in a cohort of 231 recipients) despite short-course prophylaxis being given to high-risk recipients [52]. These investigators observed that CMV pneumonitis was associated with a significantly increased risk of BOS (HR 2.19) and diminished survival (HR 1.89).

Interestingly, a prospective, randomized 11-center trial that examined the effects of 3 vs. 12 months of post-transplant valganciclovir prophylaxis for D+R−, D+R+, and D−R+ recipients showed that the 12-months prophylaxis strategy significantly diminished the incidence of CMV infection (64 % vs. 10 %), CMV disease (32 % vs. 4 %), and disease severity without any significant difference in rates of acute rejection, opportunistic infection, CMV UL97 ganciclovir-resistance mutations, or adverse events [60]. However, it remains unclear whether such prolonged prophylaxis can reduce risk for BOS.

Infection with other β(beta)-herpes viruses may also cause serious complications. The non-CMV β-herpes viruses include Epstein-Barr virus (EBV), herpes simplex virus (HSV), varicella zoster virus (VZV), and human herpes viruses 6 (HHV-6) and 7 (HHV-7). A prospective cohort study of 385 lung transplant recipients linked repetitive detection of EBV DNA in peripheral blood with the development of BOS [61], and HHV-6 or HHV-7 infection has been associated with BOS [62, 63].

Infection with community-acquired respiratory viruses (CARV) can be asymptomatic, cause mild symptoms, cause significant respiratory tract disease, or lead to acute respiratory insufficiency and death. Recovery of CARV (influenza A and B, respiratory syncytial virus, parainfluenza viruses, rhinoviruses, enteroviruses, adenoviruses, human metapneumovirus, human coronavirus, and human bocavirus) during infections suspicious for CARV in lung transplant recipients can range from 34 to 66 % [64–66], and retrospective as well as recent prospective investigations have linked CARV infections with BOS risk [64, 67–73].

Post-transplant bacterial infection is exceedingly common in recipients with prior septic lung disease (CF and non-CF bronchiectasis) and is a leading cause of death in recipients with established BOS. Botha et al. [74] reported that de novo allograft colonization with *Pseudomonas aeruginosa* was strongly associated with developing BOS within 2 years of transplant (23.4 % colonized vs. 7.7 % non-colonized), Vos et al. [75] reported that persistent *Pseudomonas* colonization was an even greater risk for BOS than de novo colonization, and Gottlieb et al. [76] found that persistent allograft *Pseudomonas* colonization in a cohort of 59 patients with CF significantly increased the prevalence of BOS. Additionally, Vos et al. [77] reported that BAL bile acid levels, neutrophils, and IL-8 levels correlated significantly with *Pseudomonas* colonization and suggested that the presence of abnormal GER and microaspiration can lead to persistent colonization with *Pseudomonas*.

Invasive fungal infections can be an important cause of morbidity and mortality in lung transplant recipients. Valentine et al. [78] reported that the diagnosis of fungal pneumonia or pneumonitis in a cohort of 160 recipients was an independent predictor of BOS with a hazard ratio of 2.1 (95 % CI 1.1–4.0) for early (0–100 days post-transplant) and 1.5 (95 % CI 1.1–1.9) for late (≥1 year) fungal pneumonia on multivariate analysis. Another study of 201 recipients reported that *Aspergillus* colonization was independently associated (multivariate Cox regression analysis) with the subsequent development of BOS (HR = 1.81; 95 % CI 1.03–3.19) and BOS-associated mortality (HR = 2.57; 95 % CI 1.19–5.55). Additionally, recipients with new or persistent *Aspergillus* colonization after developing BOS had increased risk of progression to Stage 3 BOS or death [79].

Recent observations also suggest that environmental exposures can lead to airway injury and obliteration in non-transplant patients [80–82], and higher ambient levels of pollutants have recently been linked to BOS in lung transplant recipients [83]. Additionally, airway ischemia caused by disruption of the bronchial circulation has also been suggested as a potential cause of BOS [84]. Because established OB displays variable evidence of inflammation combined with evidence of heightened innate immune responses, alloimmune reactions, autoimmunity, and fibroproliferation with airway obliteration that leads to allograft airway remodeling and loss of function, OB likely represents a final common endpoint for allograft bronchiolar injury that can be precipitated and/or driven by a variety of insults and mechanisms.

Evolving Therapies That May Stabilize or Improve Delayed/Chronic Allograft Dysfunction

Over the past decade it has become increasingly recognized that many recipients with declining lung function consistent with FEV_1 criteria for BOS can respond to certain interventions (see Chaps. 12, 14, 15, and 16) (Table 1.3). Macrolides and neo-macrolides such as the azalide, azithromycin, possess anti-inflammatory effects and inhibit IL-8 production and neutrophil recruitment, suppress bronchial inflammation, and prevent or modulate airway damage for a number of respiratory disorders [85]. Observations from many centers indicate that a substantial number of patients who develop clinical BOS respond to azithromycin and may have their lung function stabilized or significantly improved (see Chap. 15), such that some patients may no longer meet FEV_1 criteria for BOS after responding to the drug [86, 87]. Azithromycin appears to be capable of diminishing the risk of graft loss and recipient death when given to patients with established BOS [88, 89]. Additionally, the recently published, randomized prospective, placebo-controlled clinical trial conducted by Vos et al. [90] suggested that prophylactic administration of azithromycin initiated shortly after transplantation can significantly decrease the risk of developing BOS, although a significant impact on survival was not shown over the relatively brief, 2-year evaluation period.

As mentioned above, abnormal GER is highly prevalent in patients with advanced lung disease and in lung transplant recipients [37, 91], and the prevalence may increase post-transplant [39, 40]. Notably, abnormal acid GER has been strongly linked to risk for BOS (see Chap. 12). However, pharmacologic therapy with proton-pump inhibitors (PPI), although such therapy can increase the pH of gastric secretions and relieve symptoms, may have little effect on GER [41]. Indeed, PPI therapy may have negligible effect on nonacid reflux, which may contain bile acids that can be very injurious to the lung [40, 92]. Because pharmacologic suppression of gastric acid secretion may not significantly suppress abnormal GER (especially weakly acid or nonacid reflux) and microaspiration, gastric fundoplication has been investigated to a considerable degree as a means of preventing lung transplant complications and as a treatment for BOS when reflux appears to be present [93–95].

Table 1.3 Emerging phenotypes of CLAD: key features[a]

Entity	Classic BOS	RAS	NRAD
Time of onset	• Late (usually 2–3 years post-transplant, but may occur earlier)	• Tends to occur later but may occur at any time	• Usually occurs early (e.g., 3–6 months post-transplant)
Physiology	• Obstructive (FEV_1 ≤80 % of stable baseline value)	• Restrictive (e.g., FEV_1 ≤80 % and TLC ≤90 % of stable baseline values)	• Obstructive (FEV_1 ≤80 % of stable baseline value)
HRCT imaging	• Air trapping often present • Infiltrates usually not present • ±Bronchiectasis	• Parenchymal infiltrates usually present (DAD and/or fibrosis often present) • ±Bronchiectasis • ±Air trapping	• Changes of bronchiolitis (“tree-in-bud,” thickened airway walls, peribronchiolar infiltrates often present) • ±Air trapping
Histopathology	• OB (difficult to diagnose via transbronchial biopsy)	• Fibrosis (thickened septae and pleurae) • DAD often present • OB may be present	• Cellular bronchiolitis
Clinical course	• Typically progressive but may stabilize • Recipients may have coexistent chronic bacterial infection	• Tends to be relentlessly progressive (especially if early DAD on TBB) • Significantly worse prognosis than BOS	• High likelihood of significant response to azithromycin (may no longer meet FEV_1 criteria for BOS if recipient responds to azithromycin)
Other	• Usually responds poorly to pharmacologic therapies • Can have outcome similar to primary transplant following lung retransplantation	• Increased risk of RAS if new onset DAD detected >90 days post-transplant	• BAL neutrophilia (e.g., ≥15 % on differential cell count) correlates with response to azithromycin therapy

BAL bronchoalveolar lavage, *BOS* bronchiolitis obliterans syndrome, *CLAD* chronic lung allograft dysfunction, *DAD* diffuse alveolar damage, FEV_1 forced expiratory volume in 1 s, *NRAD* neutrophilic reversible allograft dysfunction, *OB* obliterative bronchiolitis, *RAS* restrictive allograft syndrome

[a]Infection, other pathologies (e.g., acute cellular rejection, lymphocytic bronchiolitis, antibody-mediated rejection), and/or other causes of allograft dysfunction (e.g., significant gastroesophageal reflux, pleural disorders, anastomotic dysfunction, obesity, thromboembolic disease, recurrent primary lung disease, etc.) must be ruled out

One case series suggests that it may prevent the appearance of BOS or prevent its progression if abnormal GER is diagnosed in patients who have developed BOS [35]. Additionally, as with the improvement in FEV_1 that has been observed with azithromycin therapy, fundoplication has been reported to lead to improved lung function such that patients can revert to BOS Stage 0 [34].

In summary, it has become clear that lung function decline that is consistent with a diagnosis of BOS can stabilize in some patients and not lead to sustained, progressive deterioration in allograft function and graft loss. Allograft functional decline that is consistent with the onset of BOS may respond to azithromycin therapy or anti-reflux surgery such that spirometric criteria for BOS are no longer met due to improved FEV_1 and clinical status. However, treatment of BOS with intensified immunosuppression or other modalities remains relatively ineffective to date, and more research into the basic pathogenetic mechanisms, preventive strategies, and treatment interventions is greatly needed.

Nomenclature and Phenotypes of Delayed-Onset Lung Allograft Dysfunction

It seems logical to use the term CLAD to indicate a late or delayed, significant decline in lung function that can be due to evolving OB as well as other causes of allograft dysfunction in the chronic setting. However, it should be recognized that CLAD (which is increasingly used to indicate a decline in FEV_1 that appears to meet criteria for BOS) may not necessarily be caused by "chronic rejection" that is mediated by classical alloimmune responses (see Chap. 3). Additionally, a number of processes may be operant simultaneously and contribute to declining allograft function. For example, the presence of significant anastomotic dysfunction combined with OB. The ability to identify characteristics that identify subsets of lung transplant recipients who have allograft function decline that meets criteria for BOS but may have specific disease mechanisms, specific triggering events and pathways, or characteristics that predict beneficial response to a specific treatment intervention can aid efforts to provide specific treatments and make key management decisions concerning specific therapies to treat BOS.

A cause of CLAD has been recently described that has characteristics that distinguish it from typical BOS/OB (Table 1.4). Sato et al. [96] identified 156/468 recipients transplanted from 1996 to 2009 who developed a clinical picture consistent with CLAD (defined as an irreversible decline in FEV_1 to <80 % of baseline), and 47 (30 %) of those diagnosed with CLAD displayed evidence of restriction (irreversible decline in total lung capacity [TLC] to <90 % of baseline) associated with thoracic imaging (HRCT) changes consistent with interstitial lung disease (ILD) and peripheral parenchymal lung fibrosis. This constellation of findings was termed restrictive allograft syndrome (RAS). Survival was worse for patients with (RAS) vs. patients with typical BOS (541 vs. 1,421 days; $p=0.0003$). Two other groups have also described a subset of BOS patients with features of restriction via

Table 1.4 Management of BOS

- Identify and treat potentially reversible non-BOS causes of impaired graft function
- Administration of neo-macrolides (e.g., azithromycin)
- Adjust maintenance immunosuppression
  - Optimize regimen
  - Switch to tacrolimus if FEV_1 decline occurred on CsA-based regimen
  - Avoid sustained, high-dose corticosteroids
- Evaluate for abnormal GER (acid and nonacid)
  - Consider fundoplication if significant GER is identified
- Screen for appearance of de novo anti-HLA antigen
  - Consider IVIG, plasma exchange, and/or rituximab if detected
- Therapies for progressive BOS refractory to other interventions
  - Total lymphoid irradiation
  - Extracorporeal photopheresis
  - Retransplantation

CsA cyclosporine A, *GER* gastroesophageal reflux, *IVIG* intravenous immunoglobulin

pulmonary function testing. Verleden et al. [97] diagnosed CLAD in 71 of 294 recipients and found that 20 (28.2 %) patients had restrictive changes on pulmonary function testing; 17 of these 20 recipients had persistent parenchymal infiltrates on HRCT, and multivariate analysis showed that a restrictive pattern on pulmonary function testing (decline in TLC in 15, decline in FEV_1 and FVC in 5 with restrictive FEV_1/FVC ratio) was associated with worse survival. Woodrow et al. [98] also identified a substantial number of recipients with CLAD who met the FEV_1 criterion for BOS and had evidence of restriction (47 of 62, 44 %) via spirometric testing (TLC data were not reported) showing forced vital capacity decline from baseline ≥20 %; however, the prevalence of parenchymal infiltrates on HRCT was similar for the restrictive vs. obstructive groups that met BOS criteria, and survival did not differ between the groups.

A more recent analysis of recipient cohorts who developed BOS by Sato et al. [99] has shown that the detection of diffuse alveolar damage (DAD) on lung biopsy specimens may have important implications for both obstructive BOS and RAS. They reported that DAD was seen at least once on TBLB in 320/720 (44 %) recipients, and early DAD (≤3 months post-transplant) was associated with a significantly increased mortality risk. They also found that bilateral lung recipients with adequate pulmonary function testing to distinguish RAS from BOS had earlier onset of BOS if early DAD was detected. Additionally, late new-onset DAD (>90 days post-transplant) was a significant risk factor for developing RAS. A review of temporal changes on lung biopsy in recipients with RAS showed that DAD tended to be followed by development of pleuroparenchymal fibroelastosis [100]. Additional characterization of a subset of patients showed that ground-glass opacities on HRCT correlated with DAD episodes, and such episodes were accompanied by a decline in lung function with subsequent stabilization during interval periods that correlated with allograft fibrosis [101].

The existence of distinct phenotypes on the basis of length of time from transplant to BOS development and the tempo of disease progression have been suggested in the literature. Those recipients with early-onset BOS may represent a group of patients that is prone to rapid progression and poor prognosis [20, 25, 102, 103]. Median survival for recipients with acute-onset BOS has been noted to be 29 vs. 58 months for later, chronic-onset BOS [104]. Additionally, Burton et al. [105] found that progression of BOS from lower to higher grade increases the risk of mortality up to threefold, and a rapid decline in FEV_1 of >20 % has been associated with worse prognosis [106]. Brugiere et al. [107] found that recipients with early-onset BOS had lower mean FEV_1, need for supplemental oxygen, and poorer graft survival than those with later-onset BOS. These observations suggest that patients with early-onset BOS represent a subset of recipients that are at risk for a more rapid decline in lung function plus a higher incidence of graft failure and death as compared to patients with late-onset BOS. However, not all patients with rapidly declining lung function associated with BOS have relentless progression; some may stabilize despite an initial rapid BOS onset and FEV_1 decline [108].

The presence of significant bronchoalveolar lavage (BAL) neutrophilia that is often associated with high-resolution computed tomographic (HRCT) changes of probable cellular bronchiolitis in patients with FEV_1 decline that meets the criterion for BOS Stage >0 has been perceived as representing a variant of BOS. These individuals are likely to respond to azithromycin therapy [88, 109], and FEV_1 may improve such that the recipient no longer meets spirometric criteria for BOS. Indeed, this reversibility, should it occur in response to azithromycin, poses an issue in terms of classifying this entity as a phenotype or subtype of BOS if criteria for BOS Stage ≥1 or even BOS-0p are eventually no longer met due to a significant therapeutic response. This phenomenon has been termed neutrophilic reversible allograft dysfunction (NRAD) [15, 88], and it has been suggested to represent a specific phenotype of CLAD. In contrast to NRAD, patients who meet BOS criteria but do not respond to azithromycin have been proposed to represent a fibroproliferative BOS phenotype [88]. Nonetheless, distinct phenotypes of BOS that are based upon specific risk factors or other parameters have yet to be firmly established, and azithromycin-unresponsive individuals may have significant variation in their underlying histopathological changes from those who respond to azithromycin.

The data from Sato et al. [96] and Verleden et al. [97] indicate that recipients with RAS may comprise a relatively specific CLAD phenotype that is distinguishable from patients with the more common BOS pattern of airflow obstruction that is usually not associated with parenchymal infiltrates. These observations suggest that HRCT imaging and lung volume determinations (and perhaps FVC and the FEV_1/FVC ratio) can be useful to differentiate recipients with the RAS phenotype from those with a typical obstructive BOS pattern when spirometric criteria for the onset of BOS are met. However, OB lesions may be present in lung specimens from recipients who develop allograft dysfunction that is consistent with a RAS phenotype [96].

Nomenclature and Classification of Allograft Dysfunction Syndromes: A Suggested Approach

The differential diagnosis of acute lung allograft dysfunction includes surgical complications, PGD, or hyperacute rejection. Early allograft dysfunction that occurs outside of the immediate postoperative period is generally caused by acute cellular rejection, lymphocytic bronchiolitis, or infection, but other entities such as vascular or humoral rejection, pleural effusion or empyema, or venous thromboembolism must be considered.

Similarly, the differential diagnosis of late or delayed chronic allograft dysfunction must include a considerable number of potential complications as discussed in Chap. 3, and the recent observations discussed above suggest that imaging and the determination of lung volumes can differentiate graft dysfunction caused by RAS from classical obstructive BOS. Distinguishing between these entities may be important in decision making (e.g., considering early listing for retransplantation for RAS that is progressive and unresponsive to therapeutic interventions), as the prognosis associated with RAS appears to be significantly worse than that associated with obstructive BOS. Additionally, HRCT imaging combined with a BAL differential cell count can identify changes (cellular bronchiolitis on HRCT, BAL neutrophilia) that identify patients with a high likelihood of having NRAD, which can improve with neo-macrolide therapy. As our knowledge of these evolving syndromes with their differing phenotypic characteristics advances, therapies may be identified that provide benefit for a specific subset of CLAD but may not have efficacy for other phenotypes.

We suggest that delayed allograft dysfunction with a persistent decline in $FEV_1 \geq 10\ \%$ of baseline can be used as a threshold value to signify the likely onset of CLAD, and such an FEV_1 decline should trigger consideration of the various entities that could cause such a decline in graft function and appropriate diagnostic testing to determine the cause(s). Imaging should be performed, and HRCT with expiratory views may provide more useful information than a routine chest radiograph. Bronchoscopy with examination of bronchial anastomoses and performance of BAL and endoscopic lung biopsies is likely to provide useful information that can be combined with clinical presentation and physical examination, imaging, and pulmonary function studies to identify and/or rule out various potential causes of CLAD. If criteria for the diagnosis of BOS are met, the various risk factors associated with BOS should be considered and appropriate testing performed to determine the most likely etiology and identify treatments that are most likely to stabilize or possibly improve allograft function (e.g., anti-reflux surgery for significant GER). This evolving classification scheme (Fig. 1.1) needs to be validated, but its adoption would allow a more precise definition of terms used to describe delayed-onset allograft dysfunction and also convey the complexity of CLAD, set a lower threshold to investigate FEV_1 decline in the chronic setting (which may allow earlier diagnosis and interventions to

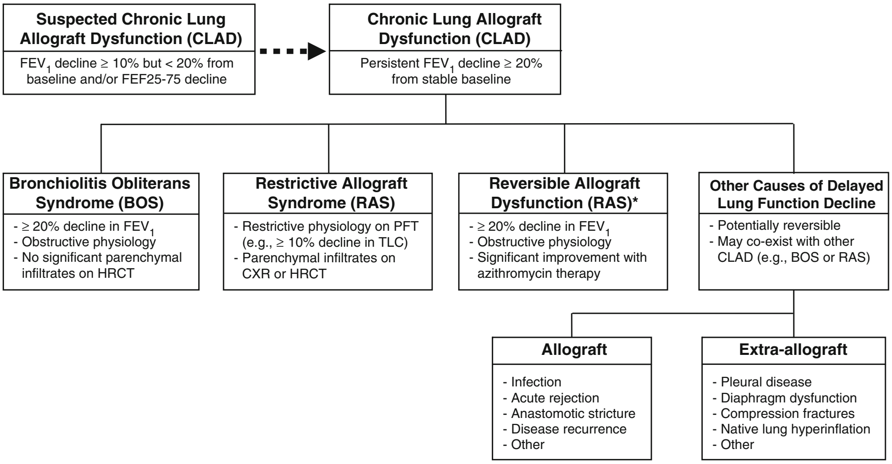

Fig. 1.1 Suggested definitions and characteristics of CLAD and its subcategories. *Decline in FEV_1 may be due to (probable cellular) bronchiolitis that can respond to azithromycin therapy such that FEV_1 significantly improves or normalizes: predictors of an increased likelihood of improvement with azithromycin include BAL neutrophilia (≥15 % neutrophils) and HRCT changes consistent with bronchiolitis (tree-in-bud opacities, peribronchiolar infiltrates, ±air trapping). *CXR* routine chest radiograph, FEF_{25-75} forced expiratory flow rate from 75 to 25 % of forced vital capacity, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *HRCT* high-resolution computed tomogram, *PFT* pulmonary function testing, *TLC* total lung capacity

preserve allograft function), and promote the evolving concept that distinct phenotypes of CLAD can be identified that may have varying prognoses and responses to therapeutic interventions.

Conclusion

Our perception of chronic allograft dysfunction is changing. While the terms OB, BOS, CLAD, and chronic rejection have been frequently used as synonymous and pertaining to allograft function due to OB, we now recognize that what we have termed BOS up to the present is actually a heterogeneous entity (e.g., RAS vs. BOS) and that (1) the term CLAD may be a better term to use for delayed allograft dysfunction, (2) CLAD can be caused by a variety of entities that have an impact on allograft function, (3) BOS is one of a number of relatively distinct CLAD entities, and (4) BOS phenotypes may better be identified according to time of onset post-transplant, rapidity of progression, underlying etiology (e.g., associated with GER, azithromycin-responsive), and response to therapies (e.g., azithromycin or anti-reflux surgery). We suggest that a new classification system with precise definitions should be created for delayed allograft dysfunction (i.e., CLAD).

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