Update in Chronic Lung Allograft Dysfunction

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KEYWORDS

• Chronic lung allograft dysfunction • Bronchiolitis obliterans syndrome • Treatment • Risk factors • Diagnosis

KEY POINTS

- The definition of chronic rejection after lung transplantation has been refined and it is now understand that there are separate obstructive and restrictive phenotypes of chronic lung allograft dysfunction (CLAD).
- Diagnosis of CLAD is made using spirometric changes; however, adjunctive modalities are evolving.
- Risk factors for CLAD include immune and nonimmune mediators.
- Retransplantation is the only effective treatment of CLAD, but there are several therapies available that may stabilize lung function.
- CLAD is the major limitation to posttransplant survival.

INTRODUCTION

Despite improvements in surgical technique, immunosuppression, and posttransplant care, and perhaps due to the significant immunogenicity of the lung compared with other solid organs, outcomes after lung transplantation lag significantly behind those of other solid organs; median survival is currently at 5.5 years, compared with 11 years for heart transplant recipients.[1,2] Chronic lung allograft dysfunction (CLAD) remains the leading cause of death and the primary limitation to long-term survival for lung transplant recipients. This article provides a review of the epidemiology, changes in diagnostics, risk factors, and clinical outcomes of this important lung transplant complication.

CHRONIC LUNG ALLOGRAFT DYSFUNCTION: HISTORICAL PERSPECTIVE, NOMENCLATURE, AND EPIDEMIOLOGY

To understand the impact of CLAD on the morbidity and mortality of lung transplant recipients, the complexity and heterogeneity of the syndrome need to be appreciated. Pathologic descriptions of chronic allograft injury after lung transplant were first described after initial attempts at lung transplantation in the 1960s and typically showed obliteration and fibrosis of small airways in the lung.[3] In one of the original series of heart-lung transplantation, surgical lung biopsy samples demonstrated evidence of obliterative bronchiolitis (OB) lesions.[4] Half of these early heart-lung recipients developed OB on biopsy samples, on

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average 11.2 months after lung transplantation.[5] The term, *bronchiolitis obliterans syndrome* (*BOS*), was established and standardized in a landmark consensus statement in 1993. BOS defines a common form of CLAD by spirometric rather than by pathologic criteria, thereby facilitating serial evaluation. The severity of BOS (grades 0–3) is determined by the extent of decrease in forced expiratory volume in the first second of expiration (FEV_1) from a patient's post-transplant baseline (**Table 1**).[6] The development of consensus grading guidelines, published by the International Society for Heart and Lung Transplantation (ISHLT), allowed clinicians and investigators at transplant centers across the world to report their experiences with BOS in a more uniform manner. The investigators of this original statement highlighted the need for ongoing refinement over time as new data became available.

In 1996, the Stanford University lung transplant program published an overall BOS prevalence of 68% among 61 lung transplant recipients and 64% in 135 heart-lung transplant recipients over a 15-year period.[7] These patients had a freedom from BOS rate of only 29% at 5 years after transplant. The University of Pittsburgh lung transplant program reported that their average time to BOS onset was 434 days.[8] Valentine and colleagues[9]'s reported a median time to BOS onset of 689 days (range 55–3404) in 89 heart-lung and 13 bilateral lung transplant recipients with freedom from BOS of 72%, 30%, and 15% at 1, 5, and 10 years, respectively.

With greater utilization of the 1993 BOS definitions, its limitations in detecting early disease were increasingly recognized by the transplant community. Several investigators noted that decline in physiologic parameters of lung function other than FEV_1 often preceded the decline in FEV_1 in patients who met diagnostic criteria for BOS.[7,9,10] For example, Valentine and colleagues[9] noted that half of all patients with biopsy-proved OB had significant declines in forced expiratory flow at 50% of forced vital capacity (FVC) (forced expiratory flow, midexpiratory phase [$FEF_{50\%}$]) 4 months prior to meeting the 1993 criteria for BOS.[9] The Stanford group found that pulmonary function tests showed significant declines in the forced expiratory flow between 25% and 75% of the FVC ($FEF_{25\%–75\%}$) prior to reduction in FEV_1.[7] Similarly, in a single-center study of 30 transplant recipients over 2 years, declines in $FEF_{25\%–75\%}$ predated the needed 20% FEV_1 decline by 112 days.[11] Reynaud-Gaubert and colleagues[10] showed reduced $FEF_{25\%–75\%}$, increase in the slope of the nitrogen washout curve, and the development of alveolar neutrophilia on bronchoalveolar lavage (BAL) all predated the decline in FEV_1 needed to define BOS grade 1. Finally, Estenne and colleagues[12] demonstrated that indices of ventilation distribution (slope of the helium and nitrogen washout curves) preceded the 20% decline in FEV_1 by a median of 6 months to 12 months. The perceived limitation in diagnostic sensitivity led to the first update of the ISHLT BOS criteria in 2002, with the addition of BOS 0p, defined as FEV_1 81% to 90% of baseline and/or $FEF_{25\%–75\%}$ less than or equal to 75% of baseline (**Table 2**).[13]

Several studies have evaluated the predictive utility of the potential BOS 0p grade. Lama and colleagues[14] demonstrated that of the patients who met the BOS 0p FEV_1 criteria, 81% developed BOS or died within 3 years. In a study of 203 bilateral lung transplant recipients, 57% of patients who met the BOS 0p FEV_1 criteria developed BOS 1 or greater within a year, compared with

Table 1
Bronchiolitis obliterans syndrome classification (1993)

Grade	Definition
BOS 0	FEV_1 80% or more of baseline
BOS 1	FEV_1 66% to 80% of baseline
BOS 2	FEV_1 51% to 65% of baseline
BOS 3	FEV_1 50% or less of baseline

Adapted from Cooper JD, Billingham M, Egan T, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society for Heart and Lung Transplantation. J Heart Lung Transplant 1993;12(5):713–6.

Table 2
Bronchiolitis obliterans syndrome classification, 2001

Grade	Definition
BOS 0	FEV_1 >90% of baseline and $FEF_{25\%–75\%}$ >75% of baseline
BOS 0p	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 2	FEV_1 51% to 65% of baseline
BOS 3	FEV_1 50% or less of baseline

Adapted from Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 2002;21(3):297–310.