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A new classification system for chronic lung allograft dysfunction

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Although survival after lung transplantation has improved significantly during the last decade, chronic rejection is thought to be the major cause of late mortality. The physiologic hallmark of chronic rejection has been a persistent fall in forced expiratory volume in 1 second associated with an obstructive ventilatory defect, for which the term bronchiolitis obliterans syndrome (BOS) was defined to allow a uniformity of description and grading of severity throughout the world. Although BOS was generally thought to be irreversible, recent evidence suggests that some patients with BOS may respond to azithromycin with $>$ 10% improvement in their forced expiratory volume in 1 second. In addition, a restrictive form of chronic rejection has recently been described that does not fit the strict definition of BOS as an obstructive defect. Hence, the term chronic lung allograft dysfunction (CLAD) has been introduced to cover all forms of graft dysfunction, but CLAD has yet to be defined. We propose a definition of CLAD and a flow chart that may facilitate recognition of the different phenotypes of CLAD that can complicate the clinical course of lung transplant recipients.
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Survival after lung transplantation remains significantly shorter than survival after transplantation of other solid organs. This disparity in survival has been attributed to the development of chronic rejection, which represents a major complication that limits the 5-year survival to approximately 55%.[1] Initial investigations that examined lung tissue from recipients with persistent decline in allograft function after lung transplantation showed histopathologic changes of obliterative bronchiolitis (OB), which was perceived to be a consequence of chronic rejection that principally occurred through alloimmune mechanisms.[2,3] However, histopathologic confirmation of OB is difficult to obtain from transbronchial lung biopsy specimens due to limited sampling of lung tissue compared with surgical lung biopsy.[4]

Hence, an International Society for Heart and Lung Transplantation (ISHLT) committee introduced the term bronchiolitis obliterans syndrome (BOS), which was originally meant to reflect chronic forced expiratory volume in 1 second (FEV_1) decline due to the development of OB.[5] The introduction of this clinical surrogate marker of chronic allograft dysfunction allowed the creation of a uniform system based on FEV_1 measurements that could be used worldwide to describe persistent decline in lung function due to progressive OB in the lung allograft. However, a number of allograft or extra-allograft abnormalities can also lead to persistent decline in FEV_1, as previously described in the 2001 BOS revision document by Estenne et al.[6]

As a consequence of new insights into the pathophysiology of BOS and the evolution of strategies to treat patients with BOS, an update of the initial statement on criteria for the diagnosis of BOS was published in 2002,[6] and a second revision is currently ready for submission after approval by the American Thoracic Society, ISHLT, and the European Respiratory Society. During the process of preparing the

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latest revision, the ISHLT, American Thoracic Society, and European Respiratory Society committee members acknowledged that a substantial cohort of patients had chronic FEV_1 decline after lung transplantation for which the previous definition of BOS was not the best descriptor.

This statement focuses on the description of additional entities that can lead to chronic FEV_1 decline after lung transplantation and proposes introduction of a new classification system which defines various terms that can be used to help the lung transplant community recognize distinct entities with important differences in their clinical manifestations and pathobiology. It is envisaged that a broadly accepted definition of chronic lung allograft dysfunction (CLAD), along with the recognition of different clinical entities that can lead to CLAD, may facilitate investigations that seek to elucidate the pathophysiologic mechanisms that lead to CLAD and thereby potentially suggest new strategies that may improve long-term survival after lung transplantation.

Lung allograft dysfunction

Lung allograft dysfunction may be an acute phenomenon (acute lung allograft dysfunction [ALAD]), leading to an acute decline in FEV_1 (with or without forced vital capacity [FVC] decline) and may be due to various conditions that affect the graft, including acute infection, pulmonary embolism, and acute rejection, among others. We acknowledge that in some of these conditions, spirometry will not be available, but ALAD may be diagnosed from other measures of acute graft dysfunction such as radiology, oxygenation status, and biopsy specimen.

Although primary graft dysfunction (PGD) is a common early cause of acute allograft dysfunction, it is a very early post-operative process for which no comparison pulmonary function is available, so by definition must sit outside the description of ALAD diagnosed by a change in FEV_1. PGD can, however, be a cause of CLAD (see below). Many conditions that cause ALAD are usually responsive to specific treatment, which may indeed restore the FEV_1 and FVC to baseline values. If, however, the pulmonary function decline is not restored to $>$ 90% of baseline and persists for 3 weeks, chronic lung allograft dysfunction (CLAD) may be suspected. Recognizing that some patients may develop β_2-agonist reversible airflow limitation,[7] we suggest measuring post-bronchodilator lung function to assess whether a particular decline in FEV_1 is fixed. Even if the FEV_1 is fully reversible with bronchodilatation, we still suggest to carefully look for possible underlying causes of FEV_1 decline.

Chronic lung allograft dysfunction

CLAD is a term that was first introduced in the lung transplant literature in 2010,[8] although no precise definition currently exists. This document will propose such a definition in the attempt to draw together some disparate notions regarding this condition and standardize its use in describing loss of lung allograft function so that data on functional decline can be uniformly collected. The proposed definition of CLAD is based on expert clinical experience, review of available data, and expert opinion. We suggest that CLAD should not be used as a synonym for BOS. We support the use of the BOS classification system where appropriate and according to the ISHLT definition, after exclusion of all other reversible causes.[6]

CLAD is an overarching term that embraces all forms of chronic lung dysfunction after transplant, and therefore, by definition, should include all cases of BOS. We recognize that individual patients may have more than one reason for declining graft function; for example, OB can manifest as BOS with associated chronic graft infection. Appropriate treatment of infection may lead to improved allograft function.

Fitting the use of the CLAD acronym to the common English meaning of the words is important; hence, an alternative definition can be "a transplanted lung that does not achieve or no longer maintains normal function for an arbitrarily defined period of time." Normal post-transplant pulmonary function is rather difficult to define because this may depend on the size-match/mismatch between donor and recipient, the quality of the donor lung(s), and the operative procedure (single vs bilateral lung transplantation).

As a consequence, patients may have a restrictive physiology (increased FEV_1/FVC ratio). We would not consider this as an abnormal lung function, and hence as CLAD. After single lung transplantation, it is suggested that the actual FEV_1 should be at least 50% of the predicted FEV_1, to be considered normal. By contrast, a lung that does not achieve normal function (for instance, due to previously severe primary graft dysfunction) could be described as having CLAD even if the FEV_1 is slowly improving but remains with a function that is significantly decreased when measured against predicted normal physiologic indices. Such a patient series with an early obstructive pulmonary function after bilateral lung transplantation was recently described by Suhling et al.[9] These recipients were older at transplantation, had significantly decreased FEV_1, increased total lung capacity (TLC), and donor organs with lower partial pressure of oxygen when ventilated with 100% oxygen before retrieval.[9] Therefore, the term CLAD may also be used in this situation, although it would most often be used to describe loss of function from the best post-transplant FEV_1 achieved once the function of the implanted allograft has stabilized.

It is suggested that the use of the term CLAD per se does not (and cannot) make any assumptions regarding the potential reversibility or irreversibility of the underlying causes of allograft dysfunction, nor is the term CLAD so specific as to justify its use as a diagnosis. CLAD is simply a descriptor of sustained lack of normal function of the transplanted lung or, more commonly, a persistent decline compared with the best post-operative FEV_1. Every effort should be made to identify the specific cause of persistent decreased function in the hope that appropriate and successful therapeutic interventions can be undertaken to restore and optimize graft function. Various conditions that may cause CLAD are described below, and a diagnostic algorithm is provided in Figure 1.