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 obliteratorive 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 (FEV1) 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 FEV1 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 FEV1, 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 2002,7 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
latest revision, the ISHLT, American Thoracic Society, and European Respiratory Society committee members acknowledged that a substantial cohort of patients had chronic FEV\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{2}-agonist reversible airflow limitation, we suggest measuring post-bronchodilator lung function to assess whether a particular decline in FEV\textsubscript{1} is fixed. Even if the FEV\textsubscript{1} is fully reversible with bronchodilatation, we still suggest to carefully look for possible underlying causes of FEV\textsubscript{1} decline.

Chronic lung allograft dysfunction

CLAD is a term that was first introduced in the lung transplant literature in 2010,\textsuperscript{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.\textsuperscript{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\textsubscript{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\textsubscript{1} should be at least 50% of the predicted FEV\textsubscript{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\textsubscript{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.\textsuperscript{9} These recipients were older at transplantation, had significantly decreased FEV\textsubscript{1}, increased total lung capacity (TLC), and donor organs with lower partial pressure of oxygen when ventilated with 100% oxygen before retrieval.\textsuperscript{7} 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\textsubscript{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\textsubscript{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.
The term “chronic” implies a certain duration of time, and in analogy with the BOS definition, we suggest a minimum of 3 weeks as a sufficiently prolonged period to label allograft dysfunction as “chronic.” This interval of at least 3 weeks is chosen arbitrarily but is inspired by the BOS definition, also using a minimum of 3 weeks as a definition for persistent decline. The challenge of the lung transplant community will be to evaluate the utility of this definition and time period and to decide whether an alternative interval would provide greater utility based on subsequent evidence.

Persistence of causes of graft dysfunction (Figure 1, specific causes) for longer than 3 weeks that may be potentially reversible may still fit this definition, and we refer specifically to azithromycin-responsive allograft dysfunction (ARAD), described below, which may take > 3 weeks of azithromycin treatment to produce a response. The detection of CLAD should stimulate a rigorous evaluation to determine the reason(s) why a lung allograft does not work or no longer works properly.

It is proposed that CLAD may not be a permanent situation, because CLAD may be reversible upon specific treatment. Despite use of the term, “chronic,” we do not advocate waiting 3 weeks before investigating the cause of declining function or persistent graft dysfunction and initiating potential therapies to improve or restore lung function. CLAD will often be diagnosed in retrospect after therapies have proved inefficient.

In contrast to the BOS classification, which is solely based on FEV₁ decline, we suggest that when CLAD is suspected or has been identified, further investigation, including full pulmonary function testing (measurement of TLC and residual volume in addition to spirometry), transbronchial biopsy specimen analysis, bronchoalveolar lavage (BAL) with total and differential cell count, and high-resolution computed tomography (HRCT) of the thorax with inspiratory and expiratory imaging may provide additional information that facilitates the identification of specific CLAD phenotypes (Figure 1, Table 1). We also suggest that a decline of
10% in FEV₁ and/or FVC from stable baseline function (suspected CLAD) should already trigger an investigation to identify a cause or causes of functional decline such as acute cellular and antibody-mediated rejection, lymphocytic bronchiolitis, and ARAD. We are aware that other therapies may prove successful in the future and that there are logical incongruities in defining a disease by its response to a particular therapy, but until such time as we have a precise etiologic cause for ARAD, the proposed terminology may at least be a correct descriptor.

Suspected CLAD, defined by a 10% drop in FEV₁ and/or FVC, might then replace BOS O-p, which was introduced in the revised BOS definition report,⁶ as a trigger for further etiologic investigations and specific treatments.

**Obstructive CLAD: BOS**

When the FEV₁ decline (≥ 20%) is not only persistent, this means in 2 measurements at least 3 weeks apart, but also obstructive (based on FEV₁/FVC ratio), we suggest that BOS should continue to be used as the preferred term to describe this phenotype of CLAD. Not every patient should or will go through a stage of suspected CLAD, because some patients may already have lost > 20% of their FEV₁ when they are diagnosed with allograft dysfunction.¹⁰ The revised definition of BOS, as given in the approved and submitted 2013 revision document, emphasizes that a decline in lung function that meets BOS criteria may be partially or even completely reversible (in contrast to previous definitions where this possibility was considered but not formally addressed) if it responds to specific treatment options (e.g., azithromycin, fundoplication, etc).

Indeed, although the 2001 revision of the BOS statement acknowledged that BOS might be reversible, reversibility was considered an exception,⁶ which is indeed logical if one assumes that BOS reflects the development of OB with irreversible small-airway obliteration. Small-airway disease is not necessarily fibrotic and irreversible, but may be (partially) reversible, especially in early stages such as ARAD. In addition, if evidence of infection is detected, effective measures to treat infection may improve lung function, and new evidence also suggests that lung function decline consistent with the diagnosis of BOS can stabilize or improve in some recipients.¹⁰,¹¹

Several groups have now shown that approximately 40% of patients with BOS respond to azithromycin with an increase in their FEV₁ of at least 10% and that some patients may experience complete reversal of their FEV₁ decline and return to BOS stage 0.¹²–¹⁴ A persistent increase in BAL neutrophil percentage has been recognized to predict an increased risk for the development of BOS.¹⁵–¹⁷ and when a BAL neutrophil percentage > 15% is detected, administration of azithromycin has been associated with a significant improvement in FEV₁ in a substantial number of patients.¹⁸,¹⁹ Other reports, however, have shown that BAL neutrophilia in the setting of BOS is mostly due to coexistent infection, which therefore needs to be carefully excluded.²⁰ In addition, the role of BAL neutrophilia in predicting the response to azithromycin is not corroborated in other studies; for instance, in the Meloni et al²¹ study, a significant FEV₁ response to azithromycin could also be demonstrated when BAL neutrophilia was not detected and vice versa.

Responders to azithromycin (defined as a FEV₁ increase of ≥ 10% after a 2–3 month treatment) were initially classified as having neutrophilic-reversible allograft dysfunction²² but may be renamed as ARAD or azithromycin-responsive BOS, keeping in mind that this phenotype can only be determined retrospectively after the decline in FEV₁ has been diagnosed and has subsequently responded to azithromycin. On the basis of these data, we suggest undertaking a 3-month trial of azithromycin in all patients who experience lung function decline consistent with BOS, with or without BAL neutrophilia. Repeat spirometry after 1, 2, and 3 months of treatment may assist in the decision regarding whether to continue or discontinue azithromycin based on physiologic response or not.

Long-term follow-up of azithromycin responders will be required to inform us whether azithromycin therapy simply

<table>
<thead>
<tr>
<th>Table 1 Emerging Phenotypes of Chronic Lung Allograft Dysfunction: Key Features⁴</th>
<th>Chronic Lung Allograft Dysfunction: Key Features⁴</th>
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<tbody>
<tr>
<td>Entity</td>
<td>Classic BOS</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td>Obstructive (FEV₁ ≤ 80% of stable baseline value)</td>
</tr>
<tr>
<td>HRCT thoracic imaging</td>
<td>Air trapping usually present</td>
</tr>
<tr>
<td>No/minimal</td>
<td>With/without bronchiectasis</td>
</tr>
<tr>
<td>With/without air trapping</td>
<td>Parenchymal/pleural fibrosis with/without OB</td>
</tr>
<tr>
<td>Histopathology</td>
<td>OB (difficult to diagnose by transbronchial biopsy specimen)</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Typically progressive but may stabilize</td>
</tr>
<tr>
<td>Recipients may have coexistent chronic bacterial infection</td>
<td>Correlates with the presence of early DAD post-transplant</td>
</tr>
<tr>
<td>Other</td>
<td>Usually responds poorly to pharmacologic therapies</td>
</tr>
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⁴Infection, 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.
delays the inevitable development of BOS, which was indeed recently suggested in a placebo-controlled trial with azithromycin during the first 2 years after lung transplantation,\textsuperscript{23} and whether the natural history is identical to that of BOS. Although azithromycin may significantly increase the chance of sudden cardiac death,\textsuperscript{24} the risk in general and especially in lung transplant patients who receive a lower dose (e.g., 3 times weekly instead of daily), remains small and should therefore be balanced against the potential benefit of azithromycin but is nevertheless worth mentioning.\textsuperscript{24}

Patients who do not respond to azithromycin likely represent a phenotype of BOS that is characterized by OB,\textsuperscript{22} although we acknowledge that OB is a pathologic diagnosis that may exist to a greater or lesser degree in any lung transplant recipient and may not be detectable until a moderate number of airways are involved. OB may coexist with any other post-transplant complication.

Imaging with HRCT may also be useful to assist in the identification of BOS phenotypes. One phenotype may show a combination of air trapping, tree-in-bud opacities, and peribronchiolar infiltrates that are compatible with the presence of bronchiolitis, and treatment with azithromycin may improve and even clear the peribronchiolar infiltrates and tree-in-bud opacities.\textsuperscript{25} Conversely, as previously reported, BOS due to OB is mostly characterized by air trapping on expiratory HRCT that is best demonstrated by mosaic attenuation when imaging is combined with a breath-hold at end-expiration.\textsuperscript{25,26}

Both of these conditions may coexist, so that such recipients may improve their FEV\textsubscript{1} > 10% upon azithromycin treatment, whereas complete reversal is unlikely to occur. These patients are more likely to have persistent BOS due to the presence of a significant degree of irreversible OB lesions.\textsuperscript{22} Whether early-onset BOS (arbitrarily defined as within 2 years after transplantation) and late-onset BOS represent the same entity remains unknown, but early-onset BOS, or BOS onset grade 2 or 3 (high-grade onset) is known to be predictive of significantly worse survival.\textsuperscript{10,27}

Other conditions have been described that may evolve and cause a decline in allograft function that fits criteria for CLAD and BOS (persistent and progressive obstructive FEV\textsubscript{1} decline). These include exudative\textsuperscript{28} or follicular\textsuperscript{29} bronchiolitis, in which lymphoid follicles in the airway wall compress the small airways but the airway mucosa itself remains normal. Thoracic HRCT may help identify these specific CLAD phenotypes that can be associated with intense airway inflammation and BAL neutrophilia.\textsuperscript{28,29}

The exact pathogenesis of these conditions when they occur after lung transplantation is unknown. Whether these represent chronic rejection processes vs local immunologic (and possibly autoimmune) phenomena remains to be elucidated.

**Restrictive CLAD: Restrictive allograft syndrome**

Recent publications have reported that some patients may experience a *persistent* decline in vital capacity and TLC that is accompanied by a decline in FEV\textsubscript{1} of > 20%, which has been termed restrictive allograft syndrome (RAS).\textsuperscript{30} Compared with BOS, we also suggest that there should be 2 pulmonary function measurements at least 3 weeks apart showing this decline and that other causes (e.g., infection, rejection, etc) should be ruled out. Depending on the relative change among the FEV\textsubscript{1}, the FEV\textsubscript{1}/FVC ratio, and the TLC, these findings may be outside the usual definition of BOS, which specifies a decline in FEV\textsubscript{1} with evidence of an obstructive ventilatory defect. When lung volumes are not specifically measured, a restrictive ventilatory defect is more firmly suggested if the FEV\textsubscript{1} and FVC simultaneously decrease while the FEV\textsubscript{1}/FVC ratio remains normal or increases above the normal range.\textsuperscript{31}

Most of the recipients with RAS reported by Sato et al had persistent (over a 3- to 6-month period) infiltrates on thoracic HRCT (ground glass opacities, interstitial infiltrates, possible honeycombing) with fibrotic changes predominant in the upper lung zone, as described previously.\textsuperscript{32,33} The presence of HRCT findings of parenchymal fibrosis is consistent with histopathologic findings from 2 autopsy case series that examined post-mortem lungs from lung transplant recipients.\textsuperscript{33,34} In addition, a recent study demonstrated that a temporal sequence of diffuse alveolar damage, followed by the development of pleuroparenchymal fibroelastosis, may occur in the histopathologic evolution of RAS.\textsuperscript{35}

Whether these infiltrates and the accompanying restrictive pulmonary function defect represent chronic rejection remains to be determined. Nonetheless, the Toronto group has clearly demonstrated the presence of diffuse alveolar damage and extensive fibrosis in the alveolar interstitium, visceral pleura, and interlobular septae, with or without scattered OB lesions, in their recipient cohort with RAS.\textsuperscript{30,35} The importance of recognizing this specific type of CLAD is suggested by the significantly worse survival of patients with RAS compared with recipients with BOS.\textsuperscript{30,31} However, this finding has yet to be substantiated by reports published by other transplant centers.

Until such time as the broad lung transplant community agrees on a validated physiologic approach to RAS, we support the concept of performing TLC measurements (preferably by body plethysmography) in routine follow-up of lung transplant patients, with, for instance, measurements twice yearly until the best FEV\textsubscript{1} is reached. The mean of the 2 best TLC measurements can then be used as the postoperative best value. In case the FEV\textsubscript{1} (with or without FVC) declines > 10% (suspected CLAD), we suggest measuring TLC as well to identify a drop of ≥ 10%, suggestive of the development of RAS. Therefore, using comprehensive pulmonary function testing plus BAL and HRCT to identify and differentiate graft dysfunction phenotypes, such as those associated with a significantly increased BAL neutrophil count and features of BOS from those associated with a predominant restrictive physiology due to parenchymal fibrosis, can facilitate the detection of CLAD phenotypes for which prognosis and treatment may vary.

Some patients who develop the RAS phenotype initially display a typical FEV\textsubscript{1} decline that is compatible with BOS
criteria but subsequently develop persistent parenchymal infiltrates later in their course that may precede the evolution of a restrictive physiology. These changes may occur over a prolonged period of time, but the development of infiltrates on HRCT seems fairly predictive of the conversion from obstructive BOS to the RAS phenotype, even though the pulmonary function decline may not be consistent with a restrictive pattern when the HRCT changes are first detected. Also patients may first develop RAS, later clear their infiltrates, and end up with classical BOS physiology.

Limitations and future needs

We suggest that the term “suspected CLAD” is a suitable alternative to BOS Stage 0-p and that the detection of a FEV₁ and/or FVC decline of > 10% from a stable, best FEV₁ and FVC value should trigger an evaluation that seeks to determine the cause(s) that explain the decline in lung function. However, we also recognize that not every patient can necessarily fit cleanly into a specific phenotype (e.g., BOS, RAS, ARAD) and that phenotypes may overlap significantly. So far, RAS is only described by 2 groups and is clearly a developing phenotype that needs further validation. Moreover, some situations are likely to still be very difficult to decipher and classify. One example would be a patient who develops multiple sequential acute rejection episodes and eventually develops a persistent decline in FEV₁ in the setting of ongoing acute rejection. Such a situation has been very well illustrated by Martinu et al with their examination of pathologic correlates of BOS in explants of patients who underwent retransplantation. Their findings seem most consistent with CLAD related to underlying persistent acute rejection. Similarly, patients who develop recurrent infectious episodes or persistent infection may have CLAD. Some infections may be occult (e.g., chlamydia) vs infections with more prominent clinical manifestations, such as Pseudomonas aeruginosa, Staphylococcus aureus, and Aspergillus fumigatus, even in the setting of development of bronchiectasis. Classification of patients with significant variability in pulmonary function over time as meeting criteria for CLAD may also prove difficult. By definition, CLAD is not present unless dysfunction is sustained for a minimum of 3 weeks. Only when alternative etiologies for impaired allograft function are ruled out, can CLAD be further phenotyped in BOS and RAS. The combination of transbronchial biopsy specimens, BAL data, and HRCT may increase the clinician’s ability to make an accurate and confident diagnosis in specific situations. In addition, the presence of significant anastomotic dysfunction due to stricture or bronchomalacia can lead to reduced FEV₁ and is perfectly in keeping with the definition of CLAD if persistent. If such a patient later develops a progressive decline in FEV₁ and/or FVC, this may still be consistent with the development of BOS or RAS upon a background of CLAD.

Many issues have yet to be resolved. These include the classification of RAS into different stages or levels of severity, as has been done for both BOS staging and for primary graft dysfunction. Another issue is the identification of HRCT imaging patterns that may be highly specific for individual CLAD phenotypes. Table 1 summarizes the key features of the BOS and RAS phenotypes of CLAD.

There are undoubtedly more non-classifiable conditions that fit under the broad umbrella of CLAD. We hope future investigations will refine this proposed model for phenotyping CLAD and identify the different pathophysiologic mechanisms underlying these phenotypes. Well-powered, collaborative multicenter studies are best suited for investigations that will improve our understanding of CLAD and will likely foster better treatment options and improve long-term survival in our lung transplant recipients.

In conclusion, we have suggested a tool for better phenotyping pulmonary function decline in lung transplant patients. We identified “acute lung allograft dysfunction” (ALAD), which may be due to acute rejection, infection, pulmonary embolism, etc., and may be reversible upon specific treatment. If reversibility is < 90% of postoperative best FEV₁ and or FVC, ALAD may become “chronic lung allograft dysfunction” (CLAD), an umbrella term used to define a persistent (at least 3 weeks), often unexplained decline in pulmonary function (FEV₁ with or without FVC) ≥ 10% from baseline (baseline defined as the average of the 2 best post-transplant values for FEV₁ and FVC obtained at least 3 weeks apart). Diagnosis of suspected CLAD should be the trigger to initiate further investigations into the cause and could therefore replace BOS 0-p in some circumstances. CLAD may still be reversible upon specific treatment (reversibility defined as an FEV₁ and/or FVC increase to > 90% of the best postoperative values), and such causes may include infection, pulmonary embolism, gastroesophageal reflux, and extra-allograft disorders such as pleural disorders, obesity, diaphragmatic dysfunction, native lung disorders, and ascites, among others.

ARAD is also part of the reversible causes, and we suggest a 3-month trial of azithromycin trial, which may improve and stabilize allograft function, before a diagnosis of CLAD due to BOS or RAS is confirmed. If the FEV₁ (with or without FVC) keeps declining (≥ 20% from baseline) despite treatment, every effort should be undertaken in all cases to further phenotype CLAD so that in the future specific therapeutic options may be developed and used.

This paper does not represent the official stance of the ISHLT.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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