CONSENSUS STATEMENT

# ISHLT Consensus Statement on Acute Lung Allograft Dysfunction (ALAD): Definition, Etiology, Diagnostic and Therapeutic Approaches, and Research Priorities

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*Abbreviations:* ACR, acute cellular rejection; ALAD, acute lung allograft dysfunction; AMR, antibody-mediated rejection; ATS, American Thoracic Society; BAL, bronchoalveolar lavage; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; CT, computerized tomography; CXR, chest x-ray; dd-cfDNA, donor-derived cell-free deoxyribonucleic acid; DSA, donor-specific antibody; ECMO, extracorporeal membrane oxygenation; ERS, European Respiratory Society; FEV1, forced expiratory volume in 1 s; HLA, Human leukocyte antigen; ISHLT, International Society for Heart and Lung Transplantation; LTx, lung transplantation; PCR, polymerase chain reaction; PGD, primary graft dysfunction; RAS, restrictive allograft syndrome; TBB, transbronchial biopsy

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## 1. INTRODUCTION

Lung transplantation (LTx) is an accepted therapy for select patients with end-stage lung disease. Since the first successful human lung transplant over 60 years ago, the field has evolved significantly, with advancements in donor selection and preservation technologies, surgical techniques, and antimicrobial prophylaxis. Despite these improvements, acute lung allograft failure and chronic lung allograft dysfunction (CLAD) continue to pose challenges to long-term patient survival.[1] Survival rates post-LTx remain low compared to other solid organ transplants, with a median survival of 6.7 years with only modest improvements observed over the past 30 years.[2]

Several distinct events during the post-LTx course contribute to lung allograft injury or impede improvement of lung allograft function after implantation. The earliest insult post-LTx is primary graft dysfunction (PGD), a form of lung injury thought to be related to ischemia and reperfusion of the lung allograft. CLAD, a later manifestation of graft dysfunction, is also defined by a specific time frame of onset, with quantifiable criteria to indicate severity and a set of established risk factors. However, LTx recipients may additionally experience acute and potentially reversible episodes of lung function decline before or after the criteria for CLAD are met. These events require investigation as they might respond to treatment, thereby potentially reducing the risk of CLAD. The term acute lung allograft dysfunction (ALAD) has been proposed to refer to these events.

Although the term ALAD has appeared with increasing frequency in the lung transplant literature over the past decade, there has been significant variation in how it has been defined, ranging from mild dysfunction to severe graft failure.[3,4] During development of CLAD definitions, the construct bronchiolitis obliterans syndrome (BOS) 0-p (the 'p' standing for 'potential' BOS) was suggested to encourage evaluation of smaller changes in spirometry.[5] In the 2019 ISHLT CLAD consensus document, the BOS 0-p term was discontinued; instead, it was recommended to start investigations of allograft dysfunction whenever the FEV1 declined by at least 10% from baseline.[5,6] Other published studies have defined the term ALAD with differing spirometric changes or clinical features. For example, ALAD has been defined as a decline in $FEV_1$ by 10% or more from prior values.[1,7] In contrast, in a series of critically ill patients with ALAD, clinical features rather than spirometry were used to define severe non-infectious ALAD, noting the lack of a consensus definition as a challenge.[8] ALAD has also been defined as infection or acute rejection, without reference to lung function.[9] Since many etiologies can contribute to an ALAD diagnosis, including infectious, immunological, and non-alloimmune causes of graft dysfunction, further confusion about how to classify ALAD has arisen.[10] As a result, the combined inconsistencies in the literature regarding the definition, evaluation tools and therapeutic strategies for ALAD pose barriers to mechanistic and clinical research alike.

At the ALAD Symposium held during the ISHLT Annual Meeting in April 2024, several needs were identified including establishing: 1) a consensus definition of ALAD, 2) an understanding of etiological factors for ALAD, 3) a universal adaptable framework for the evaluation of ALAD containing clarification of the sequence of diagnostic evaluation, 4) treatment approaches based on severity of ALAD and finally, 5) a foundation for future research and clinical trials addressing this entity. In response, the ISHLT assembled a multinational, multidisciplinary diverse group of ISHLT members to generate a consensus statement on ALAD.[11] The primary aims of this ISHLT Consensus Statement on ALAD are to standardize the nomenclature of ALAD, define its contributing etiologies, provide a suggested framework for diagnostic testing and therapeutic decision making, and identify research opportunities to facilitate collaboration and benchmarking among transplant centers in investigating the pathogenesis, possible prevention, and further treatment of ALAD.

### 1.1. Methodology

The composition of the Consensus Workgroup, including aims and specific group member involvement and roles, were approved in advance by the ISHLT Standards and Guidelines Committee. The group included transplant pulmonologists, transplant surgeons, infectious disease specialists, pathologists, pediatricians, pharmacists, and scientists from 16 different countries on 4 continents. The panel of members was organized into 6 distinct writing groups representing areas for further elucidation.

After the initial ISHLT ALAD Consensus Workgroup meeting in August 2024, a preliminary working definition of ALAD was determined by consensus voting based on elements of ALAD discussed in the workgroup meeting. Specific literature reviews were undertaken by the individual writing groups. While literature was used as a basis for recommendations, it is important to note that many of the points discussed here are based primarily on expert opinion, due to the paucity of literature on ALAD.

A panel of statements was written for assessment via the Delphi voting method[12] by workgroup members with 3 rounds of voting. These statements focused on ALAD Definition, Etiology, Diagnostics, and Therapeutics. Voting on each statement ranged from –5 (strongly disagree) to +5 (strongly agree), with 0 indicating no agreement and 4 to 5 indicating high agreement. Voting members were also allowed to abstain from voting if they felt that their level of expertise was insufficient to provide input or if unable to provide independent assessment free of conflict of interest. The mean and standard deviations for each statement in each round of voting were calculated. Abstentions were excluded from assessment of consensus. Written comments were solicited and results shared with the group between each round of voting. A consensus agreement was considered present when the mean value for a statement was ≥ 2.5 or ≤–2.5.[13] At least 90% of the workgroup voted in each Delphi round. All Workgroup members were able to contribute and critique on all aspects of the final ALAD documentation, including declarations of potential conflicts of interest. Prior to final publication, this document has been further reviewed by external expert reviewers, the ISHLT Standards and Guidelines Committee and the general ISHLT membership.

## 2. SECTION I. DEFINITION OF ALAD

CLAD is the major barrier to long-term survival post-LTx and is defined primarily by spirometric assessment. However, because substantial and potentially irreversible pathology may develop before the diagnostic criteria for CLAD are met,[6] it is critical to identify lung transplant recipients at high risk for lung function decline that might benefit from early therapeutic interventions to reverse ongoing injury. Equally, CLAD progression may result from similar acute insults after the diagnosis of CLAD is established. To this end, the syndrome of ALAD was proposed to be a sensitive and inclusive assessment of a change in lung allograft health.

In formulating the definition of ALAD, the ISHLT ALAD Consensus Workgroup has produced the final Delphi Consensus Statements (referred to subsequently in this section by bolded numbering), with their individual consensus scores (mean ± standard deviation) (Box 1).

Based on consensus voting from the Workgroup, we propose the following definition of Acute Lung Allograft Dysfunction (ALAD): **ALAD may be defined *spirometrically*, with a 10% or greater decline in $FEV_1$ (in liters) from the maximum $FEV_1$ value over the preceding 3–6 months**. **Alternatively, if spirometry is not available or feasible, ALAD can be defined *clinically* as a new or increased supplemental oxygen requirement, acute respiratory symptoms or physical exam findings, or new radiographic abnormalities (1–4.).** The Workgroup recognized that these definitions of ALAD are inclusive of a wide range of potential etiologies, which may confer differing risks for CLAD.

The group agreed that a 10% decrease in FEV1 was sufficient to indicate a significant change in allograft function (**5–6.**). This recommendation is consistent with known variability of spirometric assessments[14] and with the prior definition of BOS-0p.[5] We recommend spirometry be performed per ATS/ERS guidelines[15] because of increased reproducibility, but did not achieve consensus as to whether ALAD could be diagnosed using home spirometry results (**16.**).

The group had extensive discussions on how to best define the spirometric reference point for classifying ALAD. The group agreed that a single maximum FEV1 value was the most straightforward to allow for rapid bedside assessment. We considered FEV1 reference windows of either 3 months or 6 months (**5–6.**). If no FEV1 value is available in the last 6 months, then the most recent value should be used (**7.**) although it is recognized that many such patients will have a more chronic decline in pulmonary function. Some participants thought that a 3-month reference window was most consistent with the acute nature of ALAD and for this reason, there was stronger consensus for using a 3-month reference window. Other participants thought that a longer window would be more appropriate for a screening test,

**Box 1** Delphi Statements for Section I: Definition of ALAD.

*Note: Statements shaded in green reached consensus, whereas statements in gray did not.*

**1.** Clinically, ALAD can be defined by a 10% or greater decline in $FEV_{1,}$ but if spirometry data cannot be obtained, alternative ALAD criteria (consensus, 4.68 ± 0.55)

**2.** Clinical ALAD can be defined by a new or increased supplemental oxygen requirement in the absence of spirometric assessment. (consensus, 4.57 ± 0.65)

**3.** Clinical ALAD can be defined with concerning respiratory symptoms and exam findings in the absence of spirometric assessment. (consensus, 2.63 ± 2.05)

**4.** Clinical ALAD can be defined by radiological findings of ground glass opacities in the appropriate clinical context findings in the absence of spirometric assessment. (consensus, 2.54 ± 1.66)

**5.** Spirometric ALAD is defined as a 10% or greater decline in $FEV_1$ in the preceding 6 months. (consensus, 3.00 ± 1.84)

**6.** Spirometric ALAD is defined as a 10% or greater decline in $FEV_1$ from the maximum $FEV_1$ in the preceding 3 months. (consensus, 3.67 ± 1.63)

**7.** If spirometry data within the recommended range are not available, the most recent prior $FEV_1$ value should be used. (consensus, 3.92 ± 1.34)

**8.** Mild ALAD is spirometric ALAD without other clinical signs or symptoms of graft dysfunction. (consensus, 3.86 ± 1.21)

**9.** Moderate ALAD is spirometric ALAD with additional clinical signs or symptoms of graft dysfunction, not meeting criteria for severe ALAD. (consensus, 3.72 ± 1.67)

**10.** Severe ALAD is defined as a new or increased supplemental oxygen requirement or need for respiratory hospitalization irrespective of spirometry. (consensus, 4.58 ± 0.61)

**11.** Recovered ALAD indicates a return within 3 months of onset to within 10% of the reference $FEV_1$ prior to ALAD onset. (consensus, 3.92 ± 1.37)

**12.** Progressive spirometric ALAD indicates a subsequent further 10% decline in $FEV_1$ within 3 months from the time of ALAD onset. (consensus, 3.78 ± 1.07)

**13.** Rapidly progressive ALAD indicates that a subsequent further 10% decline in $FEV_1$ or need for hospitalization occurs within 30-days of ALAD onset. (consensus, 3.65 ± 1.20)

**14.** Patients with rapidly progressive ALAD have high risk of death. (consensus, 4.33 ± 0.99)

**15.** Persistent ALAD indicates neither recovery nor progression at 3 months. (consensus, 3.52 ± 1.46)

**16.** For diagnosis of ALAD, either in-lab or home spirometry can be used. (did not reach consensus, 1.23 ± 2.43)

**17.** ALAD may indicate the onset of CLAD. (consensus, 4.08 ± 1.57)

**18.** ALAD may develop in an individual with CLAD who previously had stable $FEV_1$ values. (consensus, 4.45 ± 0.94)

**19.** The cause of ALAD does not need to be determined for ALAD diagnosis. (consensus, 4.46 ± 0.89)

**20.** Idiopathic ALAD is characterized by an absence of any identifiable etiology after investigative evaluation or assessment of response to empiric therapy. (consensus, 4.73 ± 0.49)

**21.** ALAD should not be assessed less than 72 hours post-LTx. (consensus, 4.82 ± 0.52)

**22.** ALAD should not be assessed less than 1 month post-LTx. (did not reach consensus, 1.44 ± 3.19)

**23.** ALAD should not be assessed less than 6 months post-LTx. (did not reach consensus, -1.53 ± 3.13)

because graft dysfunction can present insidiously and a longer reference window may help ensure ALAD physiology is not missed (Figure 1). Because the maximum FEV1 value over 6 months is always greater than or equal to the maximum value over 3 months, the 6-month window is consistent with both consensus statements (**5–6.**).

Because ALAD is to be distinguished from CLAD, the recommendation of working group is to use a 3-month reference when available. We recommend caution with the diagnosis of ALAD in recipients with a 10% decline relative to a time point greater than 3 months. There is general agreement that ALAD typically develops over days to weeks and the reference maximum $FEV_1$ value over the preceding 3-months had greater consensus agreement than did the 6-month

**Figure 1**

Illustrations of ALAD diagnosis. (A) Trajectories of ALAD progression. The solid lines depict $FEV_1$ as measured by spirometry. The dotted horizontal lines indicate the 3-month reference baseline (3.0 L), a 10% decline (2.7 L), and a further 10% decline from ALAD onset. ALAD is diagnosed when the $FEV_1$ in liters has declined by 10% or more from baseline. If the $FEV_1$ recovers back to within 10% of the prior baseline, it is Recovered ALAD. If the $FEV_1$ neither recovers nor declines, it is Persistent ALAD. If the $FEV_1$ continues to decline by another 10% from the time of ALAD onset within 3 months, it is Progressive ALAD. If the additional decline occurs within 1 month, it is Rapidly Progressive ALAD. (B) ALAD Baselines. The solid line depicts $FEV_1$ as measured by spirometry, with the circles showing timepoints of spirometric assessment. This example illustrates a patient who would meet ALAD criteria using a 6-month reference baseline (maximum $FEV_1$ in 6 months), but not using a 3-month baseline. (C) ALAD can occur in the context of CLAD. The solid line depicts $FEV_1$ as measured by spirometry, with the circles showing timepoints of spirometric assessment. The shaded gray box depicts time with CLAD. This example illustrates a patient who developed ALAD which progressed to a > 20% decline consistent with CLAD onset. Several months later, the patient developed an additional ALAD episode with a > 10% decline in $FEV_1$. ALAD, acute lung allograft dysfunction; CLAD, chronic lung allograft dysfunction; $FEV_1$, forced expiratory volume in one second.

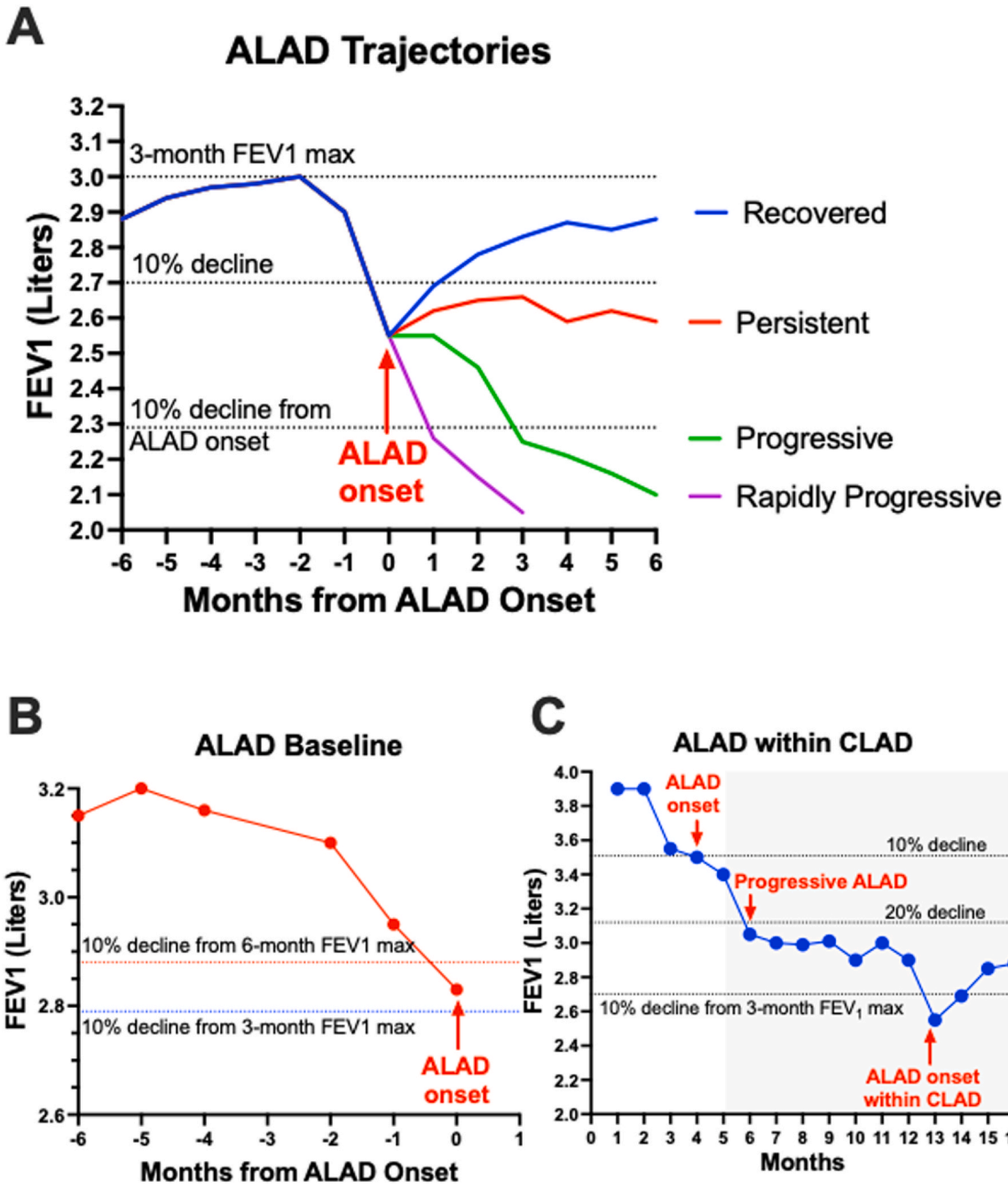


**Table 1** Summary of ALAD Grading/Subtypes

| | |
|---|---|
| ALAD | ALAD is primarily a spirometric diagnosis of a 10% or greater decline in $FEV_1$ (in liters) from the single maximum $FEV_1$ value over the preceding period of 3-6 months.<br>ALAD can also be defined clinically based on either new or increased supplemental oxygen requirement or development of concerning respiratory symptoms and examination findings. |
| Mild ALAD | Spirometric ALAD without other clinical signs or symptoms of graft dysfunction |
| Moderate ALAD | Spirometric ALAD with additional clinical signs or symptoms of graft dysfunction, not meeting criteria for severe ALAD |
| Severe ALAD | New or increased oxygen requirement or need for respiratory hospitalization, irrespective of spirometry |
| Recovered ALAD | A return within 3 months of onset to within 10% of the reference $FEV_1$ prior to ALAD onset |
| Progressive ALAD | A subsequent further 10% decline in $FEV_1$ from the time of ALAD onset within 3-months |
| Rapidly progressive ALAD | A subsequent further 10% decline in $FEV_1$ or need for hospitalization occurs within 30-days of ALAD onset |
| Persistent ALAD | Neither recovery to within >90% of the reference FEV1 prior to ALAD onset nor progression by an additional 10% at 3 months |
| Idiopathic ALAD | An absence of any identifiable etiology after investigative evaluation and/or assessment of response to empiric therapy. |

reference (.5,6). Further, because a therapy found to be effective for a 10% decline over 3-months may be less effective if given for more insidious decline, future clinical trails should consider subset analyses to validate the reference window most important for the outcome being studied. The clinical implications of different reference windows for ALAD identification will require refinement as the ALAD definition is assessed in multicenter patient cohorts with extensive clinical follow up.

Sometimes spirometry cannot be obtained in lung transplant recipients who are acutely ill. In these cases, ALAD can be defined clinically based on either new or increased supplemental oxygen requirement or the development of concerning respiratory symptoms and examination findings, in the absence of spirometric assessment. Signs and symptoms of ALAD may include cough or dyspnea, hypoxemia or need for oxygen supplementation, and opacities on CT scan or chest radiograph.[2–4] The group reached weak consensus that ALAD could be defined based on radiographic findings in an appropriate clinical context without proof of $FEV_1$ decline. We considered many different radiologic patterns in group discussions, but only specifically voted on whether ground glass opacities would be sufficient for ALAD diagnosis as it was thought that these may reflect the most acute processes. Again, future studies will be needed to validate the non-spirometric elements and radiographic patterns that identify patients at risk for ongoing allograft dysfunction.

Because diagnosing ALAD using these features involves clinical judgment, we recommend the spirometric definition of ALAD for research studies. The group emphasized in discussions that **the cause of ALAD does not need to be determined** for a patient to meet criteria for ALAD (**19.**), There is no required diagnostic workup or specific set of assessments needed for diagnosis, but when workup is completed and no specific etiologic cause of ALAD is found, this is termed idiopathic ALAD (**20.**).

We propose a nomenclature to categorize the severity and clinical patterns of ALAD (Figure 1**,** Table 1). This defined mild ALAD as spirometric change without clinical symptoms or signs (**8.**), moderate ALAD as spirometric change with additional clinical evidence of graft dysfunction (**9.**), and severe ALAD as requiring increased oxygen supplementation or hospitalization for respiratory failure (**10.**). The group also focused on clinical trajectories after ALAD diagnosis (**11–15.**). We propose definitions of recovered ALAD, persistent ALAD, progressive ALAD, and rapidly progressive ALAD based on the subsequent trajectory of FEV1 (Figure 1A).

The group reached strong consensus that detection of ALAD may be a precursor to CLAD development, acknowledging that not all ALAD etiologies may confer the same risk for CLAD. An individual identified with a 10% decline from a most recent value of >6 months has allograft dysfunction of unknown chronicity and may have progressed from ALAD to CLAD physiology. ALAD may indicate the onset of CLAD, but may similarly develop in an individual with pre-existing CLAD who previously had stable $FEV_1$ values (**17–18.**) (Figure 1C). Patients with pre-existing CLAD are eligible for a diagnosis of ALAD; for these patients, the reference FEV1 for spirometric ALAD determination are unchanged. ALAD in CLAD may be a sign of subsequent CLAD progression or an "acute on chronic" physiology. After ALAD diagnosis, the $FEV_1$ can improve, remain at the new baseline level, or progress to more severe disease. Patients with rapidly progressive ALAD have a high risk of death (**14.**).

Finally, the group discussed how early ALAD could be diagnosed after transplant. There was agreement that ALAD cannot be assessed in the first 72 h following transplant, given the overlap with PGD (**21.**). However, the group did not agree on whether ALAD could be diagnosed within 1 month of transplant (**22.**). We did not reach consensus on whether ALAD could be diagnosed within 6 months after transplant (**23.**); overall, the group thought that ALAD could likely be diagnosed in this period, but there was uncertainty of how to interpret relative spirometric changes when post-transplant FEV1 is low, as is often the case early on. The group struggled with how to best align ALAD with sufficient assessment with spirometry, particularly in those patients who have poor baseline allograft function or have prolonged index hospitalizations. We hope that future studies will clarify the potential impact of ALAD at various timepoints after lung transplantation.

## 3. SECTION II. ETIOLOGIES OF ALAD

Potential ALAD etiologies include a wide spectrum of causes at different time points post-LTx and classifying ALAD etiology into distinct subcategories may facilitate more detailed analyses of their associations with clinical outcomes.

Regarding the etiologies of ALAD, the ISHLT ALAD Consensus Workgroup has produced the final Delphi Consensus Statements (referred to subsequently in this section by bolded numbering), with their individual consensus scores (mean ± standard deviation) (Box 2).

**Box 2** Delphi Statements for Section II: Etiologies of ALAD.

*Note: Statements shaded in green reached consensus, whereas statements in gray did not.*

**1.**The etiology of ALAD can be sub-categorized as alloimmune, non-alloimmune, or idiopathic. (consensus, 4.70 ± 0.51)

**2.** Alloimmune ALAD can result from an episode of acute cellular rejection (ACR). (consensus, 4.88 ± 0.33)

**3.** Alloimmune ALAD can result from an episode of acute antibody-mediated rejection (AMR). (consensus, 4.84 ± 0.37)

**4.** Alloimmune and non-alloimmune ALAD can occur simultaneously. (consensus, 4.76 ± 0.48)

**5.** Non-alloimmune ALAD can result from an infection. (consensus, 4.84 ± 0.37)

**6.** Non-alloimmune ALAD can result from aspiration. (consensus, 4.50 ± 1.49)

**7.** Non-alloimmune ALAD can result from fluid overload. (consensus, 3.78 ± 1.97)

**8.** Non-alloimmune ALAD can result from pleural effusion. (consensus, 3.62 ± 2.09)

**9.** Non-alloimmune ALAD can result from pneumothorax. (consensus, 3.44 ± 2.05)

**10.** Non-alloimmune ALAD can result from airway complications. (consensus, 4.04 ± 1.68)

**11.** Non-alloimmune ALAD can result from diaphragm dysfunction. (did not reach consensus, 0.71 ± 2.97)

**12.** Non-alloimmune ALAD can result from respiratory muscle weakness. (did not reach consensus, 0.47 ± 2.90)

**13.** Non-alloimmune ALAD can result from frailty. (did not reach consensus, -0.09 ± 2.71)

**14.** Non-alloimmune ALAD can result from acute pain. (did not reach consensus, 0.77 ± 2.83)

**15.** Non-alloimmune ALAD can result from weight gain. (did not reach consensus, 0.61 ± 2.77)

**16.** ALAD may be unresponsive to therapy. (consensus, 4.74 ± 0.49)

**17.** Treatment response or lack of response can assist in determination of ALAD etiology. *[Very strange statement – unclear too me what is meant]* (consensus, 4.32 ± 0.79)

**18.** Rapidly progressive ALAD may be of any etiology. (consensus, 4.42 ± 1.39)

It is important to note that ALAD etiology may remain unknown despite appropriate investigations for alloimmune and non-alloimmune etiologies, in which case the term idiopathic ALAD should be used (**1.**). While stratifying ALAD into subcategories may provide a useful framework for examining associations with clinical outcomes, the working group noted that alloimmune and non-alloimmune ALAD may present concurrently and should be considered distinctly (**4.**).

Immune responses likely play a significant part in ALAD (**2–3.**). Acute cellular rejection (ACR) is a frequent complication of LTx and is associated with worse overall clinical outcomes and increased incidence of CLAD,[16] particularly with higher degrees of allograft injury.[17] ACR that is accompanied by a decline in spirometry is associated with a higher risk of CLAD and death.[18] Antibody-mediated rejection (AMR) can also be associated with a decline in spirometry.[19] Indeed, clinical AMR can have a variety of clinical presentations consistent with the proposed ALAD definition.

Non-alloimmune allograft injuries may contribute to the development of ALAD. Major non-alloimmune causes include respiratory infections, aspiration, fluid overload, pleural effusion, or pneumothorax (**5–9.**). Notably, non-alloimmune ALAD etiologies may be intrinsic or extrinsic to the allograft. Community-acquired respiratory viral infections can be associated with a decline in $FEV_1$ and the development of ACR and CLAD.[20] In some LTx recipients, viral infections associated with ALAD may result in a recovery of lung function, while others may develop accelerated CLAD (**5.**).[21] Superimposed bacterial and fungal infections have also been associated with a decline in spirometry and CLAD.[22] Several studies have shown that gastroesophageal reflux and markers of aspiration including pepsinogen A4 and bile salts in bronchoalveolar lavage (BAL) are associated with elevated BAL neutrophilia, lung dysfunction, and early CLAD (**6.**).[23–26] Fluid overload or pleural effusions can result in reduced peak lung function,[27] have been associated with ACR[28] and may result in pleural thickening or even CLAD development, especially with recurrence (**7–8.**).[27] Airway complications including ischemic airway injury, stenosis and malacia can also result in allograft dysfunction, inflammation, ACR, and predisposition to infections.[29] Although it was not specifically addressed with a Delphi statement, pulmonary thromboembolism is an important cause of an acute deterioration in lung allograft function, and should be considered in the evaluation of ALAD. It is important to note that there may be additional non-alloimmune contributors to ALAD, that are not specifically addressed here.

The group did not agree as to whether extra-thoracic contributors to graft dysfunction should be included as ALAD etiologies since these are factors that do not reflect the clinical state of the graft itself (**11–15.**). Future studies will be needed to determine if changes in FEV1 or onset of clinical symptoms due to these conditions should be considered ALAD. These conditions are common after LTx and can often be evaluated with simple, non-invasive tests. Diaphragm dysfunction, which occurs in up to 40% of LTx recipients, may be evident on chest imaging, ultrasound, or phrenic nerve conduction studies.[30] Frailty, with associated respiratory muscle weakness, can be evaluated by phenotypic or cumulative deficit models.[31] Acute pain can result in respiratory splinting and may compromise spirometric assessments. Weight gain, particularly in the first year after LTx is common and could impact spirometry and respiratory symptoms, but is rarely "acute".[32,33] These non-alloimmune conditions should be *considered* in the evaluation for ALAD etiologies, though **assessment for each of these contributors is not required for ALAD diagnosis**.[6]

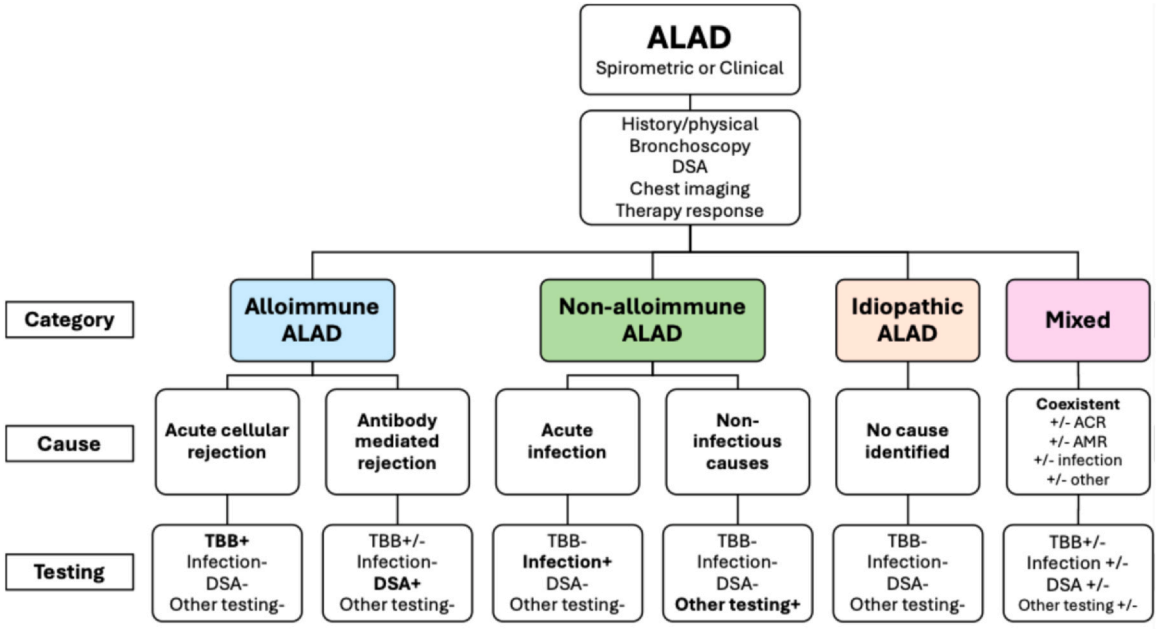
A treatment response to a suspected etiology may assist in confirming the etiology of ALAD (**17.**). For example, improvement with antibiotics suggests a bacterial etiology, while improvement with lympholytic therapy implies an immune etiology like ACR. Treatment response may be particularly helpful when prior diagnostic testing is negative, inconclusive or unable to be obtained.

It is recognized that while treatments should be targeted to identifiable etiologies, the lack of response may signal a progressive ALAD phenotype. In cases of rapidly progressive ALAD, patients may be too unstable to undergo comprehensive diagnostic testing to identify a cause. Further, significant hypoxemia might preclude invasive assessments of allograft dysfunction. Additionally, multiple etiologies may be driving rapidly progressive ALAD such that treatment should be directed at multiple potential etiologies, as delays may result in non-recovery of the allograft or death. The natural clinical history of ALAD in terms of progression, responsiveness to treatments, and recovery is yet to be fully studied.

## 4. SECTION III. DIAGNOSTIC EVALUATION OF ALAD

The successful diagnostic evaluation of ALAD is an essential element of LTx care, and one of the most critical specialized roles of the LTx clinician. A skillful approach that carefully considers the collective and individual likelihoods of each potential ALAD etiology is essential. We propose a framework for diagnostic evaluation in the

**Figure 2** Framework for consideration of diagnostic testing in ALAD and the identification of diagnostic ALAD subgroups. Multiple categories of ALAD may co-exist. ALAD, acute lung allograft dysfunctio; DSA, donor-specific antibody; TBB, transbronchial biopsy. Note that full diagnostic criteria should be applied for acute cellular and antibody-mediated rejection, but are omitted from this figure for clarity.




hopes of establishing a universal framework for ALAD evaluation (Figure 2). This provides common language and subgroup characteristics that may facilitate future studies of the mechanisms, treatment, and significance of ALAD. It is critical to note that **there is no *required* evaluation to meet the diagnostic criteria for ALAD**.

Regarding the diagnostic evaluation of ALAD, the ISHLT ALAD Consensus Workgroup has produced the final Delphi Consensus Statements (referred to subsequently in this section by bolded numbering), with their individual consensus scores (mean ± standard deviation) (Box 3).

## 4.1. History and physical examination

The initial clinical features of an ALAD presentation are often non-specific, but efforts should be made to assess for features of treatable entities. The physical examination is often similarly non-specific, but may provide information about severity and etiology. Clinicians should assess for and quantify dyspnea, cough, gastroesophageal reflux, fever, weight gain, peripheral edema, or other symptoms of respiratory disease. Potentially helpful historical elements include sick contacts, travel history, known pathogen colonization, current CLAD or baseline lung allograft dysfunction (BLAD) status,[6,34] previous detection of donor-specific antibodies, previous ACR or AMR episodes, recent immunosuppressive therapy, adherence to medical recommendations, current infection prophylaxis and adherence, and recent transfusion of blood products (**1.**).[35]

## 4.2. Investigations

### 4.2.1. Blood-based investigations

Laboratory investigation of ALAD should begin with a complete blood cell count to assess for leukocytosis, neutrophilia or neutropenia, lymphocytosis or lymphopenia, and eosinophilia.[36–38] Other basic bloodwork including renal function, liver enzymes, and electrolytes are worthwhile though rarely diagnostic (**2.**).

At this time, the working group thought that local clinical practice should guide the specific blood tests ordered during ALAD assessment. There was consensus that all patients with ALAD should have a complete blood count, assessment of immunosuppressive drug levels, and quantification of donor-specific antibodies (**2, 6.**). In the consensus discussions, the group suggested that the following tests should be *considered* for ALAD

**Box 3** Delphi Statements for Section III: Diagnostic Evaluation of ALAD.

*Note: Statements shaded in green reached consensus, whereas statements in gray did not.*

**1.** All ALAD cases should be investigated with a history and physical examination. (consensus, 4.74 ± 1.16)

**2.** All ALAD cases should be investigated with blood work, including but not limited to complete blood count with differential and immunosuppressive therapeutic drug level. (consensus, 4.88 ± 0.39)

**3.** All ALAD cases should be investigated with a chest x-ray (CXR). (consensus, 4.74 ± 0.60)

**4.** Moderate or severe ALAD should be investigated with a computed tomography (CT) of the chest. (consensus, 4.72 ± 0.73)

**5.** Mild ALAD cases may not require CT of the chest. (did not reach consensus, 1.82 ± 2.75)

**6.** All ALAD should be investigated with a blood sample for human leucocyte antigen (HLA) donor-specific antibody (DSA). *(consensus, 4.06 ± 1.48)*

**7.** All ALAD should be investigated with a blood sample for non-HLA antibody. (did not reach consensus, -0.17 ± 3.17)

**8.** Moderate or severe ALAD should be investigated with bronchoscopy. (consensus, 4.52 ± 0.71)

**9.** All ALAD should be investigated with bronchoscopy. (consensus, 3.40 ± 2.13)

**10.** Mild ALAD cases may not require bronchoscopy. (did not reach consensus, 1.90 ± 2.61)

**11.** Bronchoscopy for ALAD should include transbronchial biopsy with adequate sampling. (consensus, 3.88 ± 1.84)

**12.** Recovered ALAD treated with pulse corticosteroids alone confirms ALAD due to acute rejection. (did not reach consensus, 1.32 ± 2.55)

**13.** Recovered ALAD treated with antimicrobial therapy alone confirms ALAD due to infection. (did not reach consensus, 2.30 ± 2.37)

workup: blood quantitative cytomegalovirus (CMV) polymerase chain reaction (PCR) to assess for CMV viremia, which may be associated with pneumonitis[39,40]; HLA antibodies to assess for new or increasing levels of DSA that may suggest AMR (**6.**)[41]; and current trough immunosuppressive drug levels, which if subtherapeutic may suggest acute rejection.[42] It may also be helpful to review changes in gastrointestinal function and assess for occurrence of multiple subtherapeutic drug levels, significant variation outside the intended therapeutic range, and/or lack of adherence to the center's protocolized blood testing frequency.

### 4.2.2. Imaging

All cases of ALAD should undergo chest imaging with at least posterior-anterior and lateral CXR when feasible (**3.**). CXR may only rarely suggest specific features in the setting of ACR or AMR,[43] but can be helpful to evaluate for non-rejection elements including lobar opacities or interstitial changes, effusions, edema, pneumothorax, atelectasis, consolidation, or masses.

The Workgroup recommended consideration of CT of the chest for ALAD. Centers with access to this imaging modality may use it in all cases (**4–5.**), but where this is not the case, the group determined that CT scans are most appropriate in moderate or severe ALAD, or where there are specific features on CXR that require further evaluation. Chest CT[44] can assess for: inflammatory changes associated with severe rejection; proximal and distal airway complications; specific features of fungal infection; and CLAD features like expiratory mosaic attenuation or pleural-based, apical fibrotic changes.[45] The role of contrast in CT scans should be considered on an individual basis, balancing the diagnostic utility and risk of potential IV contrast exposure.

### 4.2.3. Bronchoscopy and respiratory tract sampling

Testing for respiratory viruses should be considered in most cases of ALAD, especially if ALAD is associated with symptoms suggestive of a viral infection, such as cough, coryza, or malaise. However, the cornerstone of the

ALAD evaluation is diagnostic flexible fiberoptic bronchoscopy. Bronchoscopy is protocolized at regular intervals in many centers[46] but we suggest a for-cause bronchoscopy in all cases of ALAD. For mild ALAD, it may be possible to defer bronchoscopy and institute empiric treatment if there is a suspected infection, or another reversible cause apparent on clinical evaluation (**8–11.**).

Bronchoscopy permits direct visualization of the large airways to assess for malacia, stenosis, or ischemic exudate as causes of ALAD, particularly early post-transplant.[29] We recommend that bronchoscopy with BAL be performed in alignment with ISHLT guidelines,[47] with appropriate microbiological and pathological assessment.

The Workgroup specifically addressed whether transbronchial biopsy should be performed during workup for ALAD. Transbronchial biopsy, with or without fluoroscopic guidance, uses forceps or cryoprobes to sample fragments of alveolar parenchyma for features of acute rejection, organizing pneumonia, acute lung injury, cytopathic changes of CMV, or other pathologic abnormalities, with the acknowledged risks of bleeding and pneumothorax. An adequate number of samples to achieve at least five evaluable parenchymal fragments for assessment, as recommended in previous guidelines,[48] should be obtained. Standardized reporting systems have been developed to limit variability in pathologic analysis, and histologic changes may be reported according to the Lung Allograft Standardized Histological Analysis (LASHA) framework.[49] In patients with advanced respiratory failure on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), the risks of bronchoscopy may preclude this investigation and empiric treatment should be considered Cryobiopsy is a newer technique which obtains larger and more representative samples of alveolar and airway tissue for histologic evaluation, although a possible increased risk of bleeding or pneumothorax has been noted.[50,51] Furthermore, the minimum number of cryobiopsies required for adequate histopathologic assessment has not yet been established. It is important to note that non-diagnostic or negative biopsies do not exclude ACR or AMR and that empiric treatment may be considered in selected cases.

#### 4.2.4. Specialized tests

Although not routinely recommended, other tests can be considered in individual scenarios for the investigation of ALAD. When AMR is being considered, specialized immunohistochemical staining may be added to conventional histology.[52] In cases where aspiration is suspected, video fluoroscopic swallowing assessment for oropharyngeal dysphagia can be performed, and analysis of transbronchial biopsies for histological signs of aspiration or BAL fluid analysis for biomarkers of aspiration including pepsinogen A4 and bile salts in BAL may be considered.[23–26,53] The group did not achieve consensus that testing for non-HLA antibodies is appropriate at this time (**7.**), given limited availability of these tests and uncertainty in interpretation of results. Emerging biomarkers, including donor-derived cell-free DNA, may also have utility in some cases of ALAD.[9] Finally, surgical lung biopsy may be considered in complex or atypical cases without a definitive diagnosis and with lack of response to empiric treatment, though this must be weighed against its risks, particularly in critically ill patients.[54–56]

### 4.3. Treatment responses

The diagnostic evaluation of ALAD is sometimes unrevealing, leaving diagnostic uncertainty. In some instances, the natural history of ALAD and the response to therapy retrospectively inform the understanding of the etiology (**12–13.**). Some cases of ALAD may spontaneously recover (particularly in mild cases) and these are of unclear prognostic significance. A complete functional response to empiric antimicrobial therapy suggests an underlying infection, while a complete functional response to empiric anti-rejection therapy e.g. pulse intravenous corticosteroids, may suggest acute rejection.[57] In many cases, particularly in critically ill patients who are unable to undergo invasive testing, multiple empiric therapies may be applied simultaneously so retrospective causal inference can be challenging.

## 5. SECTION IV: THERAPY FOR ALAD

Prompt recognition and management of ALAD provides a critical opportunity, as targeted treatment may prevent progression to irreversible graft injury and is essential for optimizing post-transplant outcomes.

The overarching therapeutic goals in ALAD management are threefold: 1. to deliver appropriate physiologic support to maintain adequate gas exchange and hemodynamic stability; 2. to identify and treat underlying causes contributing to graft dysfunction; and 3. to minimize or prevent permanent damage to the allograft. Achieving these objectives requires a nuanced and multidisciplinary approach that balances timely diagnostic evaluation with the urgency of therapeutic intervention.

**Box 4** Delphi Statements for Section IV: Therapy for ALAD.

*Note: Statements shaded in green reached consensus, whereas statements in gray did not.*

**1.** Treatment should be directed at identifiable causes of ALAD. (consensus, 4.82 ± 0.39)

**2.** Empiric broad-spectrum antibiotics should be initiated for mild ALAD. (did not reach consensus, 0.28 ± 2.37).

**3.** Empiric broad-spectrum antibiotics should be initiated for moderate ALAD. (consensus, 2.52 ± 2.11)

**4.** Empiric broad-spectrum antibiotics should be initiated for severe ALAD. (consensus, 3.90 ± 1.73)

**5.** De-escalation of antibiotics could be considered after 72 hours if culture results are negative. (consensus, 3.71 ± 1.64)

**6.** For ALAD, empiric treatment may be initiated before diagnostic testing. (consensus, 3.40 ± 1.84)

**7.** For ALAD without a known cause, empiric augmentation of immunosuppression should be initiated. (consensus, 2.69 ±1.57)

**8.** In rapidly progressive ALAD, empiric augmentation of immunosuppression to treat rejection should be initiated, without delay for diagnostic testing. (consensus, 2.69 ± 1.57)

**9.** For mild ALAD treatment, concomitant augmentation of immunosuppression and antimicrobial therapies should be considered in parallel. (did not reach consensus, -0.00 ± 2.12)

**10.** For moderate ALAD treatment, concomitant augmentation of immunosuppression and antimicrobial therapies should be considered in parallel. (did not reach consensus, 1.85 ± 1.90)

**11.** For severe ALAD treatment, concomitant augmentation of immunosuppression and antimicrobial therapies should be considered in parallel. (consensus, 3.87 ± 1.13)

**12.** For treatment of possible alloimmune ALAD, pulse steroids, intravenous gamma globulin (IVIg), lymphocyte-depleting agents (e.g., anti-thymocyte globulin or alemtuzumab), or plasma exchange may be considered. (consensus, 4.21 ± 0.72)

**13.** Patients receiving augmented immunosuppression should be closely monitored for secondary opportunistic infections. (consensus, 4.69 ± 0.51)

**14.** For patients with severe ALAD, early and aggressive respiratory support, including low- and high-flow nasal cannula, mechanical ventilation (MV), and/or ECMO, should be considered. (consensus, 4.56 ± 0.62)

**15.** ECMO should be considered in patients with severe ALAD. (consensus, 3.96 ± 1.33)

**16.** Re-transplantation could be considered for selected patients with severe ALAD. (consensus, 2.98 ± 2.23)

The ALAD Workgroup concentrated on critical aspects of clinical decision-making, including the timing of therapeutic initiation in relation to diagnostic evaluation, the use of empiric and targeted antimicrobial therapy, the role of immunosuppressive augmentation, and strategies for physiologic and respiratory support. Collectively, these principles are intended to guide evidence -informed, patient-centered care in the acute management of LTx recipients presenting with ALAD, but are not meant to be comprehensive. Although many non-infectious and non-alloimmune conditions can contribute to ALAD, as discussed above, the section on treatment focused on considerations around infectious and alloimmune ALAD. When other etiologies of ALAD are identified, appropriate therapies (for example, diuresis for volume overload or thoracentesis for pleural effusion) should be instituted.

Regarding therapeutic strategies for the management of ALAD, the ISHLT ALAD Consensus Workgroup has produced the final Delphi Consensus Statements (referred to subsequently in this section by bolded numbering), with their individual consensus scores (mean ± standard deviation) (Box 4).

There was a consensus that treatment should be directed and specific to identifiable causes of ALAD in conjunction with a thorough diagnostic evaluation as detailed in Section III above (**1.**).

## 5.1 Empiric antimicrobial therapy

Pending diagnostic confirmation empiric antimicrobial therapy is often appropriate, particularly in patients with moderate to severe presentations (**2–4, 6.**), as infectious etiologies—most notably pneumonia—represent a common and potentially treatable cause of ALAD.[10,58] The selection of empiric antibiotics should be guided by local microbiological surveillance data and the patient's infectious history, with particular consideration for coverage against resistant organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, guided by institutional susceptibility patterns.[8,10,58]

Following the collection of microbiological specimens, empiric broad-spectrum antimicrobial therapy should be reassessed and, when appropriate, de-escalated based on culture results. De-escalation should be considered within 24 h of receiving definitive culture results or reassessed by 72 h after initiation of empiric therapy. (**5.**).[10,58–60] This process may involve substituting broad-spectrum agents with narrow-spectrum antibiotics or discontinuing therapy altogether. It must be noted that empirical antimicrobial therapy can be challenging or even contraindicated, particularly in light of the increasing prevalence of fungal colonization/infection and multidrug-resistant organisms.[61]

## 5.2. Empiric augmentation of immunosuppression

The group determined that augmentation of immunosuppression should be considered in all patients with ALAD. More specifically, the group reached consensus to recommend empiric augmentation of immunosuppression in patients with severe ALAD (4.), but did not reach agreement on the use of empiric immunosuppression in cases of mild or moderate ALAD (**9–10.**). Escalation of immunosuppression is often used in conjunction with empiric antibiotic therapy (**4,11.**), particularly in cases of rapid clinical deterioration or when the patient's condition precludes diagnostic evaluation (**8.**). This recommendation is particularly relevant when an alloimmune component of ALAD is suspected, given the multiple mechanisms by which infection can potentiate alloimmune responses.[62] Careful balancing of the potential risks and benefits of empiric augmentation of immunosuppression are critical and must be considered in the context of timing of diagnostic testing. The group felt that in cases of severe ALAD, the urgency of therapeutic intervention often takes precedence over definitive etiologic clarification, despite the potential risks associated with additional immunosuppression.

Empiric augmentation of immunosuppression is recommended in cases of both confirmed and suspected alloimmune-mediated ALAD (**7,8,12.**). In these contexts, the therapeutic approach may include a range of immunomodulatory strategies such as pulse corticosteroids, intravenous immunoglobulin (IVIg), lymphocyte-depleting agents (e.g., anti-thymocyte globulin or alemtuzumab), and plasma exchange (**12.**). The choice of therapy should be guided by local availability, the clinical context, severity of presentation and patient-specific factors. It is also particularly important to be cognizant of potential risks of empiric immunosuppression and to carefully balance efficacy and safety. Rigorous monitoring for secondary opportunistic infections is essential in all patients undergoing augmented immunosuppression. (**13.**).

## 5.3. Supportive care

In patients with severe ALAD, early initiation of aggressive respiratory support should be considered, including low- and high-flow nasal cannula, non-invasive or invasive mechanical ventilation (MV), and/or ECMO (**14.**). Many episodes of ALAD are potentially reversible with timely diagnostics, appropriate supportive care, and targeted therapy. For example, 75% of ACR events are thought to be responsive to corticosteroids[63]; ALAD due to acute AMR may stabilize or improve with treatment even though long-term outcomes are often poor.[64] Although clinical trials of mechanical support are limited in the LTx population, strategies to safely incorporate the use of high-flow nasal cannula, non-invasive positive pressure ventilation, or lung protective MV support should be extrapolated from evidence in critical care and PGD literature.[65–67]

ECMO support may be considered in carefully selected individuals with severe ALAD, given rates of recoverability that approach 80% (**15.**).[8,68] In small case series of ECMO for LTx recipients, ECMO was provided in a timely manner that avoided or minimized positive pressure ventilation, and configuration strategies allowed for patients to be awake and ambulatory. If ECMO is implemented, its use should be in alignment with the recent ISHLT Consensus Statements on extra-corporeal life support[69,70] R.

The group reached consensus that re-transplantation may be considered for selected patients with severe ALAD (**16.**). However, its utility is severely constrained by the challenges of identifying appropriate candidates

**Table 2** Summary of Research Priorities for ALAD Validation, Characterization and Prognostication

- Validation and further refinement of the current ALAD definition
- Description of ALAD phenotypes based on underlying pathophysiology and disease trajectory
- Investigation of ALAD as a clinical entity in pediatric lung transplant recipients
- Further investigation of the pathophysiology of alloimmune, non-alloimmune and idiopathic ALAD
- Assessment of ALAD severity in terms of timing post-transplant and the degree of ALAD
- Short- and long-term outcomes of ALAD phenotypes, including chance of recovery and risk of progression to CLAD
- Development of predictive and prognostic models for the development of ALAD and the clinical and lung function evolution after ALAD
- Development of biomarkers for ALAD and ALAD evolution
- Development of patient-reported outcomes related to ALAD

ALAD: acute lung allograft dysfunction, CLAD: chronic lung allograft dysfunction.

coupled with generally poor post-re-transplant survival outcomes[71,72] As such, the decision to pursue re-transplantation for patients with severe ALAD should be approached with considerable caution.

# 6. SECTION V. PRIORITIES FOR FUTURE RESEARCH

## 6.1. Validation of the ALAD definition

Our proposed definition of ALAD is based largely on expert consensus and lacks a "gold-standard" diagnostic test or pathognomonic correlate. Assessing the validity of this ALAD definition is thus challenging. Syndromic definitions of diseases have used the concepts of construct (agreement between similar measures), content (biological and clinical rationale) and predictive validity (ability to predict subsequent outcomes) to derive useful classifications that have been incorporated into standard clinical practice.[73–75] Our proposed definition for ALAD meets some of these criteria, but future work is necessary to refine this initial definition. Some strengths of this proposed definition include high construct validity by virtue of leveraging objective physiological measures that are already standardized across transplant centers and high content validity based on multiple LTx expert panels agreeing that a $FEV_1$ decrease $\geq$ 10% or new or increasing hypoxemia represent clinically meaningful changes.[6,76–78] Future research is needed to determine the predictive validity of our proposed definition of ALAD in terms of CLAD, graft failure, and death (Table 2).

## 6.2. Characterization of ALAD phenotypes

It is highly relevant to study whether the type of ALAD (alloimmune, non-alloimmune, or idiopathic) has an impact on the clinical course and prognosis, and whether different causes of ALAD should be grouped or separated in future studies. It is possible that ALAD that reflects alloimmune processes (AMR or ACR) may be more likely to progress to CLAD.[79] For AMR, it is important to determine the temporal relationships between DSA and ALAD. Just as de novo DSA are associated with a greater risk for CLAD,[80] studying the associations of both pre-existing and de novo DSAs with ALAD is crucial. Similar studies could be performed with pathology-confirmed ACR. Because idiopathic ALAD is poorly understood, its clinical, pathologic, and molecular features will be of great interest. In the future, we expect that an improved understanding of the mechanistic drivers of lung allograft injury will reduce the number of ALAD episodes classified as idiopathic.

The severity and timing of ALAD are important areas for future study. Describing outcomes including hospitalization, time in the intensive care unit, and requirement for MV or ECMO are a priority. The timing of ALAD development post-LTx may influence the clinical course, treatment responses, and outcomes. Similarly, the development of ALAD in a patient with CLAD is a distinct clinical setting that needs to be investigated further.

## 6.3. The pathophysiology of ALAD

While there are likely shared mechanisms across ALAD categories, the pathophysiology of ALAD largely depends on the underlying etiology. Several early studies, examining a combination of idiopathic and non-idiopathic ALAD, have identified patterns in the immune drivers of ALAD. Cytotoxic lymphocytes, likely tissue-resident effector memory CD8[81,82] T cell populations, may prognosticate progression from ALAD to CLAD.[83,84] Specific macrophages in the BAL have

been associated with ALAD and CLAD and also found in other acute lung injury syndromes.[7] These macrophages may secrete chemokines that are known to recruit cytotoxic lymphocytes to the bronchioles and alveoli.[85] Conversely, macrophages with anti-inflammatory gene expression profile are absent in the airways and BAL of recipients with ALAD that progresses to CLAD.[84] Globally, the role of T regulatory cells in lung allograft tolerance is uncertain.[86–89] However, this population was conspicuously increased in the BAL during ALAD progression in one cohort.[84]

Others have observed changes in the small airway epithelial compartment preceding CLAD, a time at which ALAD may be concurrent. Injury repair pathways and cell cycle activation have been reported.[90] In addition, airway brushes collected before the development of CLAD are enriched for genes specific to alloantigen presentation.[91] Which airway cells are active in this process remain to be elucidated, though club cells[92] and basal cells[93] are likely implicated. More investigation is needed, with validation of these findings across broader patient populations. It is also unclear whether idiopathic ALAD is truly a separate category, or whether it manifests from subclinical or unrecognized infection, rejection or gastroesophageal reflux.

Overall, it will be important to gain a better understanding of ALAD mechanisms and whether there are common pathways involved in graft injury agnostic to etiology. There are both molecular and clinical subsets of ALAD recipients with differing rates of progression to CLAD.[84,94] Future research should focus on discovering and validating ALAD immune and airway epithelial cell phenotypes and should include multi-omics studies and molecular phenotyping of pulmonary compartments. Studies should be enriched for resolving ALAD as comparisons in this group may identify plausible targets for treatment.

## 6.4. ALAD prognostication

There are two main goals in ALAD prognostication: predicting the development of ALAD and predicting lung function trajectory after an episode of ALAD or after therapeutic interventions. The lack of a standardized definition for ALAD is one of the key barriers to understanding ALAD consequences. Additionally, although in some cases increased risk for subsequent CLAD has been described,[18,83–85,95] there remains variable predictive validity to identify patients whose ALAD will progress to CLAD. It is quite possible that some underlying etiologies of ALAD will have differing CLAD risk and additional studies are needed to clarify this. Furthermore, there is likely additional heterogeneity based on ALAD timing after transplant, number of ALAD episodes, and whether ALAD occurs in the presence of pre-existing lung function decline. Better tools are needed to understand which patients with ALAD will have poor clinical outcomes. A more granular understanding of ALAD pathogenesis will help in this regard. For both prediction of the development of ALAD and prognostication of post-ALAD trajectories, all available clinical and diagnostic data should be included in the modeling. Further, models should consider the predictive and prognostic impact of biomarkers of allograft injury. The incorporation of biomarkers and advanced cellular and molecular profiling techniques may increase the validity and generalizability of prediction and prognostic models. Finally, harnessing new advances in machine learning, artificial intelligence[96] and bioinformatics will help to address many of the limitations inherent in current methods employed in studies of ALAD prediction and prognostication.

## 6.5. ALAD as a clinical endpoint

ALAD can be a risk factor for CLAD,[18,97] with more than 50% of ALAD cases progressing to CLAD in some reports[84] and only 20% of recipients with BOS 0-p are free from CLAD or death over the following 3 years.[98] In contrast, the predictive value of single or repeated ALAD episodes may not be high when multiple etiologies are included.[97] Nevertheless, because the median time to CLAD after lung transplant approaches 5 years, ALAD may be an important early surrogate endpoint for CLAD prevention trials. As such, time from initiation of a study intervention to development of ALAD could be considered a possible endpoint. More importantly, targeted enrollment of LTx recipients with ALAD in CLAD prevention trials may serve as a strategy to enrich the study population for recipients at higher risk for CLAD. Finally, clinical trials investigating interventions for acute rejection (ACR, AMR) should endeavor to incorporate ALAD into the trial design as a subset analysis.

## 6.6. Future research tools for ALAD

An essential component of improving our understanding of ALAD is rigorous clinical, translational, pre-clinical, and mechanistic research. The development of robust multi-center clinical databases that accurately capture

longitudinal data on pulmonary function testing, oxygenation, imaging, and other key clinical parameters is paramount. Once collected, these data should be queried in multicenter analyses and subjected to robust bioinformatics approaches, including artificial intelligence-enhanced algorithms to reveal new associations and refine the ALAD definition and phenotyping criteria.

Further development and evaluation of home spirometry and emerging tools like oscillometry may allow more sensitive and frequent assessments of lung function.[99–101] Moreover, future work needs to investigate the application of the definitions from this consensus document in recipients under 18 years of age.

Translational research should continue to employ peripheral blood, BAL, and transbronchial biopsies to assess genomic, transcriptomic, proteomic, cellular, and other drivers and biomarkers of ALAD pathogenesis.[102–104] Novel samples, such as exhaled breath condensate or airway brushings, may reveal new biomarkers.[91,105] Standardized protocols for sample collection, processing, storage, and tracking are critical to ensure consistency and comparability within and between centers.[102,106] Importantly, we strongly advocate for biological sample collection and molecular biomarker incorporation in LTx clinical trials.

One of the most promising translational research areas in LTx is diagnostics, where emerging biomarkers have the potential to help determine ALAD etiologies and prognosis. Chief among these is donor-derived cell-free DNA (dd-cfDNA), a marker which is increased during periods of allograft damage and has excellent negative predictive value but limited specificity.[9] dd-cfDNA may be most helpful in ruling out graft damage in instances where extra-pulmonary confounders such as muscle weakness, pain, obesity, or large airway complications are being considered. The real-world clinical utility of dd-cfDNA for ALAD assessment requires further evaluation. In addition, we expect that tissue-based molecular assays, including phospho-S6 ribosomal protein to assess for AMR,[107] gene signatures from airway brushings or endobronchial biopsies[107–110] for rejection, or other circulating biomarkers (like mitochondrial DNA), will play a larger role in ALAD evaluation in the future,

It will be important to establish reliable in vitro and in vivo models of injuries relevant to ALAD, to elucidate key underlying mechanisms and to identify new therapeutic targets to interrupt ALAD pathogenesis and prevent subsequent graft loss. Ex vivo studies employing human cells extracted from whole lungs (immune, epithelial, endothelial, fibroblasts, or other) or precision-cut lung slices[111,112] derived from lung allografts - at bronchoscopy, surgery, or explant - may be particularly helpful to dissect the molecular underpinnings of ALAD. Ex vivo lung perfusion using intact human lungs remains an excellent platform for mechanistic analysis.[113] In addition, animal models remain vital for validating observational and in vitro findings and evaluating potential therapeutics.[114] Small animal models, such as mouse orthotopic LTx, allow for sophisticated studies leveraging transgenic or knockout strains,[115–118] while large animal models more closely mimic human anatomy and physiology.[119] Assessment of lung function in animals by plethysmography or air-flow detection,[120] blood gas measurements[119] and (micro CT) imaging[121] may allow longitudinal monitoring of transplant endpoints and could help extrapolate animal data to human ALAD.

By integrating clinical, translational, in vitro and animal research, more accurate prognostic markers and targeted interventions can be developed to improve long-term outcomes of patients with ALAD.

## 7. CONCLUSION

The consensus reached through this Delphi process represents a critical step in addressing the uncertainties surrounding ALAD. By establishing a standardized definition, recognizing key etiologies, and outlining diagnostic and therapeutic approaches, this document provides a foundation for both clinical practice and future research. The standardized framework will facilitate multicenter collaboration, enhance patient management strategies, and improve outcomes of LTx recipients. However, the validity of the currently proposed definitions needs to be rigorously validated. Future studies should assess its construct, content, and predictive validity and long-term clinical outcomes. Research is also needed to characterize the heterogeneity of ALAD phenotypes and their respective trajectories, clarify pathophysiological mechanisms and validate novel biomarkers. Continued translational and mechanistic studies, alongside the development of robust clinical databases and experimental models, will be essential to advance our understanding of ALAD pathophysiology and improve clinical care of patients with ALAD.

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None.

## DISCLOSURES

See Appendix 1.

## APPENDIX 1. AUTHOR AND REVIEWER RELEVANT RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (WITHIN LAST 24/12)

| Committee Member Name | Employment | Consultant | Speakers Bureau | Ownership/ Partnership/ Principal | Personal Research | Institutional, Organizational, or Other Financial Benefit | Expert Witness |
|---|---|---|---|---|---|---|---|
| Stephen Juvet | N/A | BlueRock Therapeutics Sanofi | N/A | N/A | N/A | Boehringer Ingelheim (grant paid to institution) | N/A |
| Ciara Shaver | N/A | N/A | CareDx | N/A | N/A | CareDx (grant paid to institution) | N/A |
| Alberto Benazzo | N/A | N/A | N/A | N/A | N/A | Grants provided by XVIVO and Therakos | N/A |
| Saskia Bos | N/A | Therakos | Therakos, Novartis, Sanofi | N/A | N/A | N/A | N/A |
| David Darley | Lung Transplant Unit, St Vincent's Hospital Sydney | N/A | N/A | N/A | N/A | The St Vincent's Hospital Curran Foundation (philanthropy to institution) | N/A |
| Tara Fallah | Johnson and Johnson | N/A | N/A | N/A | N/A | N/A | N/A |
| John Greenland | N/A | Adra Therapeutics | N/A | N/A | N/A | Therakos (grant paid to institution) | N/A |
| Kieran Halloran | N/A | Advisory board: AstraZeneca | N/A | N/A | N/A | Involved in investigator-initiated research studies partly funded by Thermo Fisher scientific and Natera | N/A |
| Tereza Martinu | N/A | Trove Therapeutics, Inc. Sanofi | N/A | N/A | N/A | Sanofi Inc. (grant paid to institution) APCBio Innovations (research material) | N/A |
| Eric Morrell | N/A | N/A | N/A | N/A | N/A | Natera (grants paid to institution) | |
| Federica Meloni | N/A | N/A | Therakos | N/A | N/A | N/A | N/A |
| Anja Roden | N/A | Advisory Board: AstraZeneca, Agilent | N/A | N/A | N/A | N/A | N/A |
| Justin Rosenheck | N/A | N/A | Natera (speaker fees) | N/A | N/A | N/A | N/A |
| Laurie Snyder | Duke University | Transmedics, AstraZeneca, Pulmocide | N/A | N/A | N/A | N/A | N/A |
| Rade Tomic | N/A | TFF Pharmaceuticals | N/A | N/A | N/A | N/A | N/A |
| Katherine Vandervest | N/A | N/A | N/A | N/A | N/A | Natera (grant paid to institution) | N/A |

## References

1. Christie JD, Van Raemdonck D, Fisher AJ. Lung Transplantation. N Engl J Med 2024;391:1822-36.

2. Chambers DC, Perch M, Zuckermann A, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult lung transplantation report - 2021; Focus on recipient characteristics. J Heart Lung Transpl 2021;40:1060-72.

3. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. J Heart Lung Transpl 2014;33:127-33.

4. Snell GI, Westall GP, Paraskeva MA. Immunosuppression and allograft rejection following lung transplantation: evidence to date. Drugs 2013;73:1793-813.

5. Estenne M, Hertz MI. Bronchiolitis obliterans after human lung transplantation. Am J Respir Crit care Med 2002;166:440-4.

6. Verleden GM, Glanville AR, Lease ED, et al. Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transpl 2019;38:493-503.

7. Moshkelgosha S, Duong A, Wilson G, et al. Interferon-stimulated and metallothionein-expressing macrophages are associated with acute and chronic allograft dysfunction after lung transplantation. J Heart Lung Transpl 2022;41:1556-69.

8. Trindade AJ, Gannon WD, Stokes JW, et al. Surviving white-out: how to manage severe noninfectious acute lung allograft dysfunction of unknown etiology. Transpl Direct 2022;8:e1371.

9. Keller M, Sun J, Mutebi C, et al. Donor-derived cell-free DNA as a composite marker of acute lung allograft dysfunction in clinical care. J Heart Lung Transpl 2022;41:458-66.

10. Mazo C, Pont T, Ballesteros MA, et al. Pneumonia versus graft dysfunction as the cause of acute respiratory failure after lung transplant: a 4-year multicentre prospective study in 153 adults requiring intensive care admission. Eur Respir J: J Eur Soc Clin Respir Physiol 2019;54.

11. Juvet S, Benden C, Calabrese F, et al. Acute Lung Allograft Dysfunction (ALAD): From Bench to Bedside. International Society for Heart and Lung Transplantation 44th Annual Meeting. Prague, Czechia. 2024.

12. Holey EA, Feeley JL, Dixon J, Whittaker VJ. An exploration of the use of simple statistics to measure consensus and stability in Delphi studies. BMC Med Res Method 2007;7:52.

13. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. J Clin Epidemiol 2014;67:401-9.

14. Rozas CJ. Goldman AL: daily spirometric variability: normal subjects and subjects with chronic bronchitis with and without airflow obstruction. Arch Intern Med 1982;142:1287-91.

15. Bhakta NR, McGowan A, Ramsey KA, et al. European Respiratory Society/American Thoracic Society technical statement: standardisation of the measurement of lung volumes, 2023 update. Eur Respir J: J Eur Soc Clin Respir Physiol 2023;62.

16. Todd JL, Weigt SS, Neely ML, et al. Prognosis and risks for probable chronic lung allograft dysfunction: a prospective multicenter study. Am J Respir Crit care Med 2025;211:239-47.

17. Keller MB, Tian X, Jang MK, et al. Higher molecular injury at diagnosis of acute cellular rejection increases the risk of lung allograft failure: a clinical trial. Am J Respir Crit care Med 2024;209:1238-45.

18. Davis WA, Finlen Copeland CA, Todd JL, Snyder LD, Martissa JA, Palmer SM. Spirometrically significant acute rejection increases the risk for BOS and death after lung transplantation. Am J Transpl 2012;12:745-52.

19. Levine DJ, Glanville AR, Aboyoun C, et al. Antibody-mediated rejection of the lung: a consensus report of the International Society for Heart and Lung Transplantation. J Heart Lung Transpl 2016;35:397-406.

20. Kumar D, Erdman D, Keshavjee S, et al. Clinical impact of community-acquired respiratory viruses on bronchiolitis obliterans after lung transplant. Am J Transpl 2005;5:2031-6.

21. Trindade AJ, Chapin KC, Gannon WD, et al. Clinical course of SARS-CoV-2 infection and recovery in lung transplant recipients. Transpl Infect Dis 2022;24:e13967.

22. Permpalung N, Liang T, Gopinath S, et al. Invasive fungal infections after respiratory viral infections in lung transplant recipients are associated with lung allograft failure and chronic lung allograft dysfunction within 1 year. J Heart Lung Transpl 2023;42:953-63.

23. D'Ovidio F, Mura M, Tsang M, et al. Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. J Thorac Cardiovasc Surg 2005;129:1144-52.

24. Urso A, Leiva-Juarez MM, Briganti DF, et al. Aspiration of conjugated bile acids predicts adverse lung transplant outcomes and correlates with airway lipid and cytokine dysregulation. J Heart Lung Transpl 2021;40:998-1008.

25. Zhang CYK, Ahmed M, Huszti E, et al. Bronchoalveolar bile acid and inflammatory markers to identify high-risk lung transplant recipients with reflux and microaspiration. J Heart Lung Transpl 2020;39:934-44.

26. Ramendra R, Duong A, Zhang CYK, et al. Airway pepsinogen A4 identifies lung transplant recipients with microaspiration and predicts chronic lung allograft dysfunction. J Heart Lung Transpl 2024;43:973-82.

27. Joean O, Kayser MZ, Valtin C, Ewen R, Gottlieb J. Characteristics and clinical implications of pleural effusions after lung transplantation: a retrospective analysis of 195 thoracocenteses in 113 patients. Clin Transpl 2021;35:e14267.

28. Bergin CJ, Castellino RA, Blank N, Berry GJ, Sibley RK, Starnes VA. Acute lung rejection after heart-lung transplantation: correlation of findings on chest radiographs with lung biopsy results. AJR Am J Roentgenol 1990;155:23-7.

29. Crespo MM, McCarthy DP, Hopkins PM, et al. ISHLT Consensus Statement on adult and pediatric airway complications after lung transplantation: definitions, grading system, and therapeutics. J Heart Lung Transpl 2018;37:548-63.

30. Eltonsy AM, Amlani K, Schleicher M, McCurry KR, Mehta AC. Diaphragmatic palsy following lung transplantation. Eur Respir Rev 2024;33.

31. Swaminathan AC, McConnell A, Peskoe S, et al. Evaluation of frailty measures and short-term outcomes after lung transplantation. Chest 2023;164:159-68.

32. Singer LG, Brazelton TR, Doyle RL, Morris RE, Theodore J. International Lung Transplant Database Study G: weight gain after lung transplantation. J Heart Lung Transpl 2003;22:894-902.

33. Jomphe V, Belanger N, Beauchamp-Parent C, et al. New-onset obesity after lung transplantation: incidence, risk factors, and clinical outcomes. Transplantation 2022;106:2247-55.

34. Liu J, Jackson K, Weinkauf J, et al. Baseline lung allograft dysfunction is associated with impaired survival after double-lung transplantation. J Heart Lung Transpl 2018;37:895-902.

35. Bertram A, Fuge J, Suhling H, et al. Adherence is associated with a favorable outcome after lung transplantation. PLoS One 2019;14:e0226167.

36. Tague LK, Scozzi D, Wallendorf M, et al. Lung transplant outcomes are influenced by severity of neutropenia and granulocyte colony-stimulating factor treatment. Am J Transpl: J Am Soc Transpl Am Soc Transpl Surg 2020;20:250-61.

37. Kaes J, Van der Borght E, Vanstapel A, et al. Peripheral blood eosinophilia is associated with poor outcome post-lung transplantation. Cells 2020;9.

38. He X, Luo Z, Han Y, Yu J, Fang S, Guo L. Correlation analysis of the peripheral blood lymphocyte count and occurrence of pneumonia after lung transplantation. Transpl Immunol 2023;78:101822.

39. Snyder LD, Finlen-Copeland CA, Turbyfill WJ, Howell D, Willner DA, Palmer SM. Cytomegalovirus pneumonitis is a risk for bronchiolitis obliterans syndrome in lung transplantation. Am J Respir Crit Care Med 2010;181:1391-6.

40. Kotton CN, Kumar D, Manuel O, et al. The Fourth International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation. Transplantation 2025;109:1066-110.

41. Hachem RR, Kamoun M, Budev MM, et al. Human leukocyte antigens antibodies after lung transplantation: primary results of the HALT study. Am J Transpl 2018;18:2285-94.

42. Ryu JH, Choi S, Lee HJ, Kim YT, Kim YW, Yang J. Low early posttransplant serum tacrolimus levels are associated with poor patient survival in lung transplant patients. Ann Thorac Med 2019;14:186-91.

43. Kundu S, Herman SJ, Larhs A, et al. Correlation of chest radiographic findings with biopsy-proven acute lung rejection. J Thorac Imaging 1999;14:178-84.

44. Gotway MB, Dawn SK, Sellami D, et al. Acute rejection following lung transplantation: limitations in accuracy of thin-section CT for diagnosis. Radiology 2001;221:207-12.

45. Glanville AR, Verleden GM, Todd JL, et al. Chronic lung allograft dysfunction: definition and update of restrictive allograft syndrome-a consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transpl 2019;38:483-92.

46. Fricke K, Sievi NA, Schmidt FP, Schuurmans MM, Kohler M. Efficacy of surveillance bronchoscopy versus clinically indicated bronchoscopy for detection of acute lung transplant rejection: a systematic review and meta-analysis. ERJ Open Res 2024;10.

47. Martinu T, Koutsokera A, Benden C, et al. International Society for Heart and Lung Transplantation consensus statement for the standardization of bronchoalveolar lavage in lung transplantation. J Heart Lung Transpl 2020.

48. Stewart S, Fishbein MC, Snell GI, et al. Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transpl 2007;26:1229-42.

49. Calabrese F, Roden AC, Pavlisko E, et al. Lung allograft standardized histological analysis (LASHA) template: a research consensus proposal. J Heart Lung Transpl 2022;41:1487-500.

50. Luo Y, Li SP. Transbronchial cryobiopsy versus transbronchial forceps biopsy for acute cellular rejection detection in lung transplantation: a meta-analysis. Arch De Bronconeumol 2024;60:698-704.

51. Loor K, Culebras M, Sansano I, et al. Lung allograft transbronchial cryobiopsy for critical ventilated patients: a randomised trial. Eur Respir J: J Eur Soc Clin Respir Physiol 2023;61.

52. Aguilar PR, Carpenter D, Ritter J, et al. The role of C4d deposition in the diagnosis of antibody-mediated rejection after lung transplantation. Am J Transpl: J Am Soc Transpl Am Soc Transpl Surg 2018;18:936-44.

53. Torous VF, Basler D, McEnery C, Astor T, Ly A. Utilization of Oil Red O staining for assessing aspiration risk in lung transplant patients: a multidisciplinary prospective study with clinical practice insights. Cancer Cytopathol 2023;131:30-6.

54. Weill D, McGiffin DC, Zorn Jr. GL, et al. The utility of open lung biopsy following lung transplantation. J Heart Lung Transpl 2000;19:852-7.

55. Choong CK, Haddad FJ, Huddleston CB, et al. Role of open lung biopsy in lung transplant recipients in a single children's hospital: a 13-year experience. J Thorac Cardiovasc Surg 2006;131:204-8.

56. Chaparro C, Maurer JR, Chamberlain DW, Todd TR. Role of open lung biopsy for diagnosis in lung transplant recipients: ten-year experience. Ann Thorac Surg 1995;59:928-32.

57. Fuehner T, Simon A, Dierich M, et al. Indicators for steroid response in biopsy proven acute graft rejection after lung transplantation. Respir Med 2009;103:1114-21.

58. Banga A, Sahoo D, Lane CR, et al. Characteristics and outcomes of patients with lung transplantation requiring admission to the medical ICU. Chest 2014;146:590-9.

59. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and treatment of adults with community-acquired pneumonia. an Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit care Med 2019;200:e45-67.

60. Tabah A, Bassetti M, Kollef MH, et al. Antimicrobial de-escalation in critically ill patients: a position statement from a task force of the European Society of Intensive Care Medicine (ESICM) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Critically Ill Patients Study Group (ESGCIP). Intensive care Med 2020;46:245-65.

61. Aguado JM, Silva JT, Fernandez-Ruiz M, et al. Management of multidrug resistant Gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. Transpl Rev (Orlando) 2018;32:36-57.

62. D'Orsogna L, van den Heuvel H, van Kooten C, Heidt S, Claas FHJ. Infectious pathogens may trigger specific allo-HLA reactivity via multiple mechanisms. Immunogenetics 2017;69:631-41.

63. Aboyoun CL, Tamm M, Chhajed PN, et al. Diagnostic value of follow-up transbronchial lung biopsy after lung rejection. Am J Respir Crit care Med 2001;164:460-3.

64. Witt CA, Gaut JP, Yusen RD, et al. Acute antibody-mediated rejection after lung transplantation. J Heart Lung Transpl 2013;32:1034-40.

65. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342:1301-8.

66. Bellani G, Laffey JG, Pham T, et al. Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE Study. Am J Respir Crit care Med 2017;195:67-77.

67. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. N Engl J Med 2015;372:2185-96.

68. Stokes JW, Gannon WD, Trindade AJ, et al. Extracorporeal membrane oxygenation for respiratory failure during readmission after lung transplantation. Chest Crit Care 2023;1:100016.

69. Martin AK, Mercier O, Bottiger B, et al. ISHLT consensus statement on the perioperative use of ECLS in lung transplantation: Part III: postoperative considerations. J Heart Lung Transpl 2025.

70. Martin AK, Mercier O, Fritz AV, et al. ISHLT consensus statement on the perioperative use of ECLS in lung transplantation: Part II: intraoperative considerations. J Heart Lung Transpl 2024.

71. Rucker AJ, Nellis JR, Klapper JA, Hartwig MG. Lung retransplantation in the modern era. J Thorac Dis 2021;13:6587-93.

72. Harhay MO, Cherikh WS, Toll AE, et al. Epidemiology, risk factors, and outcomes of lung retransplantation: an analysis of the International Society for Heart and Lung Transplantation Thoracic Transplant Registry. J Heart Lung Transpl 2022;41:1478-86.

73. Kendell R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. Am J Psychiatry 2003;160:4-12.

74. Angus DC, Seymour CW, Coopersmith CM, et al. A framework for the development and interpretation of different sepsis definitions and clinical criteria. Crit Care Med 2016;44:e113-21.

75. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama 2016;315:801-10.

76. M E, JR M, A B, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart lung Transpl: Publ Int Soc Heart Transpl 2002;21:297-310.

77. Meyer KC, Raghu G, Verleden GM, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. Eur Respir J 2014;44:1479-503.

78. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J 2022;60.

79. Brunet-Ratnasingham E, Yellamilli S, Guo R, et al. Persistent and progressive acute lung allograft dysfunction is linked to cell compositional and transcriptional changes in small airways. J Heart Lung Transpl 2025;44(9):1482-92.

80. Tikkanen JM, Singer LG, Kim SJ, et al. De Novo DQ donor-specific antibodies are associated with chronic lung allograft dysfunction after lung transplantation. Am J Respir Crit care Med 2016;194:596-606.

81. Moshkelgosha S, Levy L, Safavi S, et al. Emergence of a senescent and inflammatory pulmonary CD4(+) T cell population prior to lung allograft failure. Sci Adv 2025;11:eadp9052.

82. Snyder ME, Finlayson MO, Connors TJ, et al. Generation and persistence of human tissue-resident memory T cells in lung transplantation. Sci Immunol 2019;4.

83. Weigt SS, Wang X, Palchevskiy V, et al. Gene expression profiling of bronchoalveolar lavage cells preceding a clinical diagnosis of chronic lung allograft dysfunction. PLoS One 2017;12:e0169894.

84. Calabrese DR, Ekstrand CA, Yellamilli S, et al. Macrophage and CD8 T cell discordance are associated with acute lung allograft dysfunction progression. J Heart Lung Transpl 2024;43:1074-86.

85. Shino MY, Todd JL, Neely ML, et al. Plasma CXCL9 and CXCL10 at allograft injury predict chronic lung allograft dysfunction. Am J Transpl 2022;22:2169-79.

86. Gauthier JM, Harrison MS, Krupnick AS, Gelman AE, Kreisel D. The emerging role of regulatory T cells following lung transplantation. Immunol Rev 2019;292:194-208.

87. Li W, Gauthier JM, Higashikubo R, et al. Bronchus-associated lymphoid tissue-resident Foxp3+ T lymphocytes prevent antibody-mediated lung rejection. J Clin Investig 2019;129:556-68.

88. Salman J, Ius F, Knoefel AK, et al. Association of Higher CD4(+) CD25(high) CD127(low), FoxP3(+), and IL-2(+) T Cell Frequencies Early After Lung Transplantation With Less Chronic Lung Allograft Dysfunction at Two Years. Am J Transpl 2017;17:1637-48.

89. Beber SA, Moshkelgosha S, White M, et al. The CD8(+) T cell content of transbronchial biopsies from patients with a first episode of clinically stable grade A1 cellular rejection is associated with future chronic lung allograft dysfunction. J Heart Lung Transpl 2024;43:1654-64.

90. Dugger DT, Fung M, Hays SR, et al. Chronic lung allograft dysfunction small airways reveal a lymphocytic inflammation gene signature. Am J Transpl 2021;21:362-71.

91. Mohanty RP, Moghbeli K, Singer JP, et al. Small airway brush gene expression predicts chronic lung allograft dysfunction and mortality. J Heart Lung Transpl 2024;43:1820-32.

92. M N, K S, TN C, O A, GC R. Decreased serum and bronchoalveolar lavage levels of Clara cell secretory protein (CC16) is associated with bronchiolitis obliterans syndrome and airway neutrophilia in lung transplant recipients. U S 2002:1264-9.

93. Khatri A, Todd JL, Kelly FL, et al. JAK-STAT activation contributes to cytotoxic T cell-mediated basal cell death in human chronic lung allograft dysfunction. JCI Insight 2023;8.

94. Lu K, Bradford MC, Wang X, et al. The prognostic value of single and repeated ≥10% FEV(1) declines for chronic lung allograft dysfunction. J Heart Lung Transpl 2025;44:681-5.

95. Weigt SS, Derhovanessian A, Liao E, et al. CXCR3 chemokine ligands during respiratory viral infections predict lung allograft dysfunction. Am J Transpl 2012;12:477-84.

96. Ronen L, Keshavjee S, Sage AT. Advancing lung transplantation through machine learning and artificial intelligence. Curr Opin Pulm Med 2025;31:381-6.

97. Lu K, Bradford MC, Wang X, et al. The prognostic value of single and repeated >/=10% FEV(1) declines for chronic lung allograft dysfunction. J Heart Lung Transpl 2025;44:681-5.

98. Lama VN, Murray S, Mumford JA, et al. Prognostic value of bronchiolitis obliterans syndrome stage 0-p in single-lung transplant recipients. Am J Respir Crit care Med 2005;172:379-83.

99. Cho E, Wu JKY, Birriel DC, et al. Airway oscillometry detects spirometric-silent episodes of acute cellular rejection. Am J Respir Crit Care Med 2020;201:1536-44.

100. Darley DR, Nilsen K, Vazirani J, et al. Airway oscillometry parameters in baseline lung allograft dysfunction: associations from a multicenter study. J Heart Lung Transpl 2023;42:767-77.

101. Odisho AY, Liu AW, Maiorano AR, et al. Design and implementation of a digital health home spirometry intervention for remote monitoring of lung transplant function. J Heart Lung Transpl 2023;42:828-37.

102. Martinu T, Koutsokera A, Benden C, et al. International Society for Heart and Lung Transplantation consensus statement for the standardization of bronchoalveolar lavage in lung transplantation. J Heart Lung Transpl 2020;39:1171-90.

103. Shtraichman O, Diamond JM. Emerging biomarkers in chronic lung allograft dysfunction. Expert Rev Mol Diagn 2020;20:467-75.

104. Pradère P, Zajacova A, Bos S, Le Pavec J, Fisher A. Molecular monitoring of lung allograft health: is it ready for routine clinical use? Eur Respir Rev 2023;32.

105. Wijbenga N, Mathot BJ, van Pel R, et al. The ability of an electronic nose to distinguish between complications in lung transplant recipients. Am J Transpl 2024.

106. Brocard S, Morin M, Dos Santos Brito Silva N, et al. Description and first insights on a large genomic biobank of lung transplantation. Eur J Hum Genet 2025;33:304-11.

107. Lunardi F, Vedovelli L, Pezzuto F, et al. Assessing the role of phosphorylated S6 ribosomal protein in the pathological diagnosis of pulmonary antibody-mediated rejection. J Heart Lung Transpl 2024;43:403-13.

108. Halloran K, Parkes MD, Timofte IL, et al. Molecular phenotyping of rejection-related changes in mucosal biopsies from lung transplants. Am J Transpl: J Am Soc Transpl Am Soc Transpl Surg 2020;20:954-66.

109. Halloran K, Parkes MD, Timofte I, et al. Molecular T-cell-mediated rejection in transbronchial and mucosal lung transplant biopsies is associated with future risk of graft loss. J Heart Lung Transpl 2020;39:1327-37.

110. Greenland JR, Wang P, Brotman JJ, et al. Gene signatures common to allograft rejection are associated with lymphocytic bronchitis. Clin Transpl 2019;33:e13515.

111. Niroomand A, Hirdman G, Mittendorfer M, Bolukbas D, Olm F, Lindstedt S. 371) An Ex Vivo Model of Acute Rejection Using Precision Cut Lung Slices. J Heart Lung Transplant 2023;42:S176.

112. Kollareth DJM, Sharma AK. Precision cut lung slices: an innovative tool for lung transplant research. Front Immunol 2024;15:1504421.

113. Iske J, Hinze CA, Salman J, Haverich A, Tullius SG, Ius F. The potential of ex vivo lung perfusion on improving organ quality and ameliorating ischemia reperfusion injury. Am J Transpl: J Am Soc Transpl Am Soc Transpl Surg 2021;21:3831-9.

114. Lama VN, Belperio JA, Christie JD, et al. Models of lung transplant research: a consensus statement from the National Heart, Lung, and Blood Institute workshop. JCI Insight 2017;2.

115. Mesaki K, Juvet S, Yeung J, et al. Immunomodulation of the donor lung with CRISPR-mediated activation of IL-10 expression. J Heart Lung Transpl 2023;42:1363-77.

116. Figueiredo C, Chen-Wacker C, Salman J, et al. Knockdown of swine leukocyte antigen expression in porcine lung transplants enables graft survival without immunosuppression. Sci Transl Med 2024;16:eadi9548.

117. Okazaki M, Krupnick AS, Kornfeld CG, et al. A mouse model of orthotopic vascularized aerated lung transplantation. Am J Transpl: J Am Soc Transpl Am Soc Transpl Surg 2007;7:1672-9.

118. Lin X, Li W, Lai J, et al. Five-year update on the mouse model of orthotopic lung transplantation: Scientific uses, tricks of the trade, and tips for success. J Thorac Dis 2012;4:247-58.

119. Mariscal A, Caldarone L, Tikkanen J, et al. Pig lung transplant survival model. Nat Protoc 2018;13:1814-28.

120. De Vleeschauwer S, Jungraithmayr W, Wauters S, et al. Chronic rejection pathology after orthotopic lung transplantation in mice: the development of a murine BOS model and its drawbacks. PLoS One 2012;7:e29802.

121. Heigl T, Kaes J, Aelbrecht C, et al. The nature of chronic rejection after lung transplantation: a murine orthotopic lung transplant study. Front Immunol 2024;15:1369536.