



# Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment—A consensus report from the Pulmonary Council of the ISHLT

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The outcomes of transplantation vary widely by organ. Lung transplantation (LTx) has rather poor long-term outcome, with a current median post-transplant survival of 6.0 years.<sup>1,2</sup> Survival after organ transplantation is limited by both graft-related and non-graft-related factors. Allograft failure remains the leading cause of morbidity and mortality across all organ groups and is the major cause of death, accounting for >40% of deaths beyond the first year post-LTx.<sup>1,2</sup>

Our understanding of the patterns and pathophysiology of lung allograft dysfunction has evolved over time. Relatively early in the history of LTx, the lung transplant community, through the International Society for Heart and Lung Transplantation (ISHLT), recognized the need to develop a standard approach to classification of persistent

allograft dysfunction. In 1993, Cooper et al<sup>3</sup> introduced the first definition of “bronchiolitis obliterans syndrome” (BOS) as the key manifestation of lung allograft dysfunction. BOS, a clinical syndrome, based on spirometry, was suggested to be the clinical correlate of bronchiolitis obliterans (BO), thought to be the pathologic hallmark of chronic rejection.<sup>3</sup> BOS was identified as a persistent decline in forced expiratory volume in 1 second (FEV<sub>1</sub>) of ≥20%, compared with the reference FEV<sub>1</sub>, defined as the mean of the 2 best post-operative FEV<sub>1</sub> measurements taken at least 3 weeks apart<sup>3</sup> and after exclusion of other known pulmonary and extrapulmonary causes of FEV<sub>1</sub> decline. Since the original report by Cooper et al, a revised definition by Estenne et al has been published, incorporating a new stage, “BOS 0-p,” characterized by a 10% to 20% drop in FEV<sub>1</sub>, signifying potential BOS.<sup>4</sup> The intention of this new stage was to trigger early investigations and therapy with the hope of preventing further allograft dysfunction. More recently, a consensus guideline on the diagnosis and treatment of BOS was published that

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evaluated the existing literature and used the GRADE system to demonstrate the lack of evidence for most therapies for BOS.<sup>5</sup>

It has become apparent that the diagnosis of BOS requires further refinement. Some patients who had been diagnosed with BOS proved to have reversible allograft dysfunction after specific treatments, such as management of gastroesophageal reflux<sup>6</sup> and addition of a neomacrolide antibiotic, usually azithromycin.<sup>7,8</sup>

In addition, different patterns of lung function decline have been described in the last decade. Sato et al identified a progressive decline in pulmonary function, which was restrictive in nature rather than obstructive, and was accompanied by pleural changes and/or interstitial fibrosis on imaging studies.<sup>9</sup> This led to the introduction of the term “restrictive allograft syndrome” (RAS), which was initially described as a chronic, persistent restrictive decline in pulmonary function (decline in total lung capacity of at least 10% compared with the mean of the 2 best post-operative values) in the context of a decline in FEV<sub>1</sub> of  $\geq 20\%$ , often with persistent opacities on computed tomography (CT) scan of the chest.<sup>10</sup>

As a consequence of these and other observations supporting the heterogeneity within BOS, the term chronic lung allograft dysfunction (CLAD), first introduced by Glanville,<sup>11</sup> has been proposed as an umbrella term to describe the clinical manifestations of a range of pathologic processes in the airway and parenchymal compartments of the lung allograft that lead to a significant and persistent deterioration in lung function (with or without chest radiologic changes) and occur  $>3$  months after LTx.<sup>12,13</sup>

The lack of a consensus definition of CLAD and how it relates to BOS has been problematic. Factors including the varied timing and reproducibility of spirometry and the frequent presence of potentially reversible conditions, such as infection, pleural effusion, or acute rejection, that subsequently fail to improve with treatment may result in lack of agreement about the presence and timing of onset of CLAD.<sup>14</sup> Furthermore, some authors have used the term CLAD as a synonym for BOS, or a combination of BOS and RAS, whereas others proposed to use CLAD for every possible post-transplant decline in FEV<sub>1</sub>.<sup>12</sup>

As a consequence, the Pulmonary Council of the ISHLT assembled a group of experts to create a robust description for the term CLAD that would encompass its definition, etiology, phenotypes, pathology, treatment, and outcome. It was acknowledged that the lack of literature available on this specific topic mandated the generation of a consensus report based on expert opinion.

The primary aim of this consensus report is to standardize the nomenclature of CLAD and its clinical phenotypes to facilitate collaboration among centers investigating the pathogenesis, prevention, and treatment of CLAD.

## Definition of CLAD

CLAD is defined as a substantial and persistent decline ( $\geq 20\%$ ) in measured FEV<sub>1</sub> value from the reference

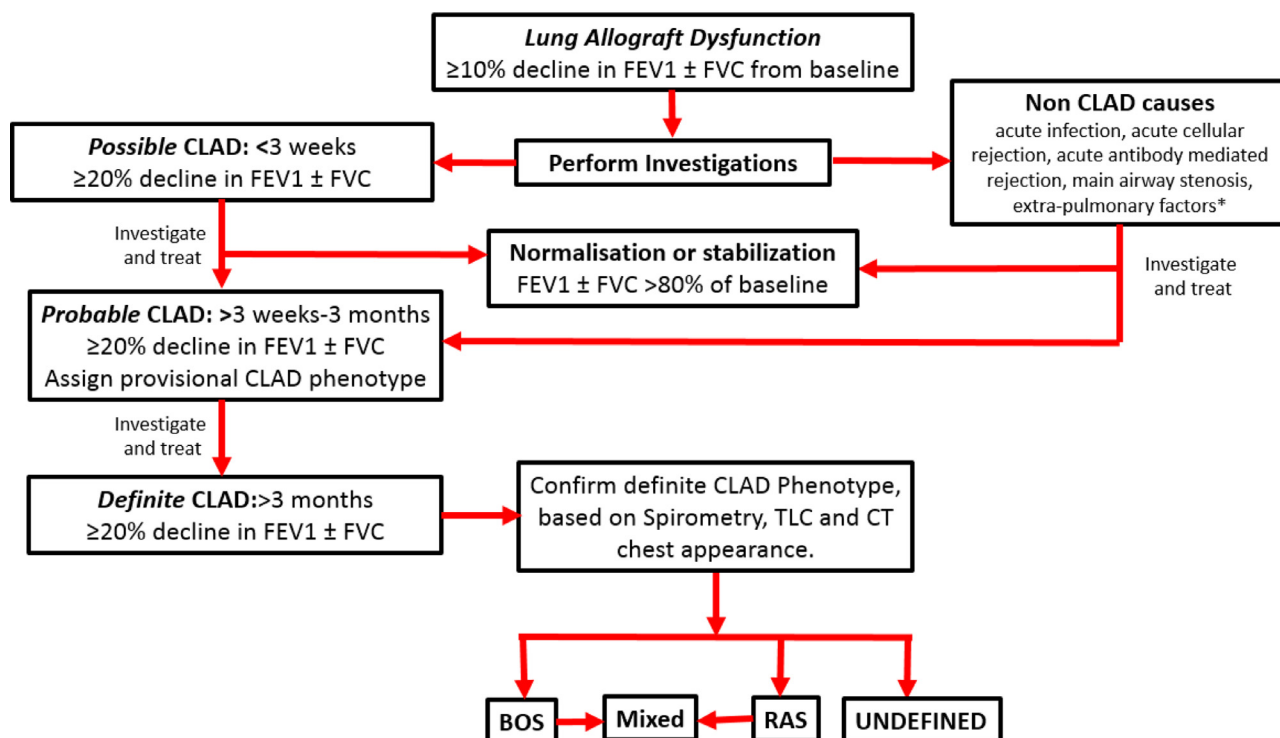
(baseline) value. The baseline value is computed as the mean of the best 2 post-operative FEV<sub>1</sub> measurements (taken  $>3$  weeks apart). CLAD can present either as a predominantly obstructive ventilatory pattern, a restrictive pattern, or a mixed obstructive and restrictive pattern that is not explained by other conditions as outlined in Table 1 or as a combination of these.<sup>11,12,15</sup>

The critical level of change in lung function is a  $\geq 20\%$  fall from baseline FEV<sub>1</sub> with or without a change in forced vital capacity (FVC), to qualify for “possible” CLAD, although it is accepted that most centers will trigger a series of investigations at a  $\geq 10\%$  threshold for “potential” CLAD (Figure 1), recognizing that this threshold falls outside the normal day-to-day variability of FEV<sub>1</sub>.<sup>16</sup> Prompt investigations should be performed to exclude the causes that may respond to intervention (Table 1). If lung function parameters remain impaired on a second reading at least 3 weeks after the first  $\geq 20\%$  fall from baseline and after adequate treatment of secondary causes such as infection, acute cellular/antibody-mediated rejection, or airway stenosis has been implemented, then a diagnosis of “probable” CLAD can be made. CLAD staging (as proposed in Table 2) and clinical sub-typing into phenotypes (Table 3) should be performed at this stage to stratify potential investigations and therapies, including entry into clinical trials if available. It was the consensus of the writing group to no longer use the classical BOS staging but to change to a CLAD staging (from CLAD 0 to 4), which seems more appropriate now that different phenotypes of allograft dysfunction have been described. CLAD Stage 3 was adapted ( $>35\%$  to  $50\%$ ) and a Stage 4 ( $\leq 35\%$ ) was introduced to better reflect differences in prognosis and to allow further clinical studies with specific CLAD stages. Moreover, it was also decided to no longer include a Stage 0-p, which was only introduced into the BOS staging system to trigger further investigations. Instead, it is now advised to start investigations whenever the FEV<sub>1</sub> declines by  $\geq 10\%$  from baseline. CLAD is “confirmed” if the physiologic abnormalities (i.e., FEV<sub>1</sub> decline of  $\geq 20\%$ ) persist for 3 months after the first value is taken (Figure 1). Further investigation to exclude any treatable causes or complications of therapy may be warranted at any stage. Infection, acute rejection (cellular or antibody-mediated), and aspiration are all relevant factors to consider when diagnosing the definitive presence and timing of the onset of CLAD. These entities are all known risk factors for acute allograft injury and subsequent CLAD. For a diagnosis of CLAD in the setting of recent infection, rejection, or aspiration, clinically appropriate therapies must be completed, and we would advise a prolonged course (at least 8 weeks) of neomacrolide therapy (usually azithromycin) in patients not already on such therapy. Although these therapies should have clinically “eliminated” the acute insult, if the allograft function fails to recover or continues to deteriorate beyond 3 months, then CLAD can be confirmed (definite CLAD).<sup>5</sup> The date of onset of CLAD is defined as the date at which the first value of FEV<sub>1</sub>  $\leq 80\%$  of baseline is recorded.<sup>4,5</sup> By definition, if lung function returns to  $>80\%$  of baseline after therapy, then the diagnosis of CLAD is not sustained

**Table 1** Processes and Diseases That May Lead to Chronic Loss of Allograft Function and Are *Not* Included in Current Definition of CLAD

- A. Factors where recalculation/resetting of the FEV<sub>1</sub> reference value may be valid (if FEV<sub>1</sub> remains stable for at least 6 months):
1. Decreasing lung function due to the normal aging process.
  2. Surgical factors.
    - Transplant lung resection, chest-wall surgery, phrenic nerve damage.
  3. Mechanical factors.
    - Persistent pleural effusion.
    - Persistent lung edema due to significant kidney/heart/liver failure.
    - Airway stenosis.
    - Myopathy, neuropathy, and Parkinson disease.
    - Weight gain.
    - Native lung hyperinflation after single-lung transplant.
  4. Localized infection with chronic scarring.
    - Abscess/empyema/mycetoma.
- B. Factors that cannot be differentiated easily from CLAD and do not ever allow recalculation/resetting of the FEV<sub>1</sub> reference value:
1. Any from (A) above where there is not a period of at least 6 months of stability.
  2. Infiltration with tumor.
  3. Infiltration of the allograft with proven disease recurrence from the underlying transplant indication (e.g., LAM, sarcoidosis, etc.).
  4. Drug or other induced pulmonary toxicity (e.g., sirolimus, methotrexate, amiodarone, radiotherapy).
  5. Pulmonary arterial strictures or emboli.
  6. Acute/subacute generalized infection.
  7. Acute/subacute cellular or antibody-mediated rejection.
  8. Acute/subacute effects of aspiration.
- C. Failing to reach normal predicted lung function (i.e., low FEV<sub>1</sub> reference value such that FEV<sub>1</sub> is  $\leq 80\%$  of the recipient predicted value). This situation may include an age difference between donor and recipient where older donor lungs are implanted or when an intra-operative allograft reduction surgery/lobectomy is performed.

CLAD, chronic lung allograft dysfunction; FEV<sub>1</sub>, forced expiratory volume in 1 second; LAM, lymphangioleiomyomatosis.



**Figure 1** Flowchart of evolution of CLAD. The date of onset of CLAD is defined as the date at which the first value of FEV<sub>1</sub> ± FVC  $\leq 80\%$  of baseline was recorded, provided subsequent values remain at  $\leq 80\%$  of baseline. Undefined indicates patients who do not fit in the current definitions of BOS, RAS, and mixed phenotypes (see Table 3). Asterisk (\*) indicates non-CLAD causes, as described in Table 1. BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CT, computerized tomography; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; RAS, restrictive allograft syndrome; TLC, total lung capacity.

**Table 2** CLAD Staging

| Stage  | Spirometry   |
|--------|--|
| CLAD 0 | Current FEV <sub>1</sub> >80% FEV <sub>1</sub> baseline    |
| CLAD 1 | Current FEV <sub>1</sub> >65–80% FEV <sub>1</sub> baseline |
| CLAD 2 | Current FEV <sub>1</sub> >50–65% FEV <sub>1</sub> baseline |
| CLAD 3 | Current FEV <sub>1</sub> >35–50% FEV <sub>1</sub> baseline |
| CLAD 4 | Current FEV <sub>1</sub> ≤35% FEV <sub>1</sub> baseline    |

CLAD, chronic lung allograft dysfunction; FEV<sub>1</sub>, forced expiratory volume in 1 second. Once CLAD is diagnosed, staging is performed according to the decline in FEV<sub>1</sub>, compared with baseline. The date of onset of CLAD is defined as the date at which the first value of FEV<sub>1</sub> ≤80% of baseline was recorded when subsequent values taken at least 3 weeks (and for definite CLAD up to 3 months) apart also fell below the threshold. The same principle holds for each stage.

(Figure 2A). These time intervals are unavoidably arbitrary and experience-based, as no hard evidence supports a time threshold for determination of when physiologic changes become permanent.

We do not recommend passive waiting to achieve a confirmed diagnosis of CLAD. Rather, active investigations and therapies should be employed and graft function monitored frequently. Every opportunity should be sought for a useful therapeutic intervention. Reassessment is a valuable tool to confirm staging and phenotype at 3 months and comparison should be made with initial staging and phenotype at CLAD onset, which occasionally may evolve quickly (e.g., from BOS to RAS).

In some circumstances, CLAD may be partly reversible upon treatment (Figure 2B), suggesting that the observed graft dysfunction was partly due to inflammation, and not only to airway or parenchymal/pleural fibrosis, which are thought to cause permanent damage.<sup>17</sup> An acutely reversible condition, such as acute infection and even acute rejection, may exist in conjunction with developing early CLAD. These 2 conditions are not mutually exclusive, and it is the net sum of persistent effects after a full course of therapy that determines whether a firm diagnosis of CLAD can be established.

## CLAD phenotypes

The most common manifestation of CLAD is the development of airflow limitation, caused by BO, which will continue to be termed BOS. The diagnostic criteria remain largely as previously elaborated.<sup>4,5</sup> Briefly, obstruction is defined by a fall in FEV<sub>1</sub> ≥20% (compared with baseline) and associated with other indices of airflow limitation (Table 3), without persistent radiologic pulmonary opacities (as defined in what follows).

Up to 30% of patients with CLAD develop a restrictive defect.<sup>10,18</sup> In the presence of persistent radiologic pulmonary opacities, this will continue to be called “restrictive allograft syndrome” (RAS) (Table 3). RAS (previously called restrictive [R]-CLAD) is defined physiologically by: (1) a persistent ≥20% decline in FEV<sub>1</sub> (± FVC) compared with the reference or baseline value; (2) a decrease in total lung capacity (TLC) to ≤90% compared with baseline, defined as the average of the 2 measurements obtained at the same time as or very near to the best 2 post-operative FEV<sub>1</sub> measurements; and (3) the presence of persistent opacities on chest imaging (chest X-ray [CXR] and/or computed tomography [CT]). Restriction should be diagnosed by a ≥10% decline in TLC relative to baseline. The potential role of an FVC decline ≥20% from baseline as a surrogate marker for restriction<sup>20</sup> is addressed further in the RAS consensus report.<sup>21</sup> If, despite appropriate therapeutic efforts, both features (restrictive physiology and CXR/CT opacities) persist after 3 months, then the diagnosis of definite CLAD with the phenotype of RAS is confirmed.

Given the uncertainty inherent in relying solely on spirometry to diagnose a restrictive ventilatory defect, we strongly recommend measuring TLC by body plethysmography to confirm a suspected diagnosis in all cases unless specific contraindications exist. In this regard, obtaining a baseline TLC at 3 and 6 months post-transplant in addition to a high-resolution CT (HRCT) at 6 months will provide a clinically useful baseline. FEV<sub>1</sub>/FVC ratio per definition increases to >0.7 with a restrictive process, but such changes are difficult to interpret in some situations. For

**Table 3** Basic Phenotypes of Chronic Lung Allograft Dysfunction

|                        | Obstruction <sup>a</sup> (FEV <sub>1</sub> /FVC <0.7) | Restriction <sup>b</sup> (TLC decline ≥10% from baseline) | CT opacities <sup>c</sup> |
|------------------------|---|---|---------------------------|
| BOS                    | Yes   | No  | No                        |
| RAS                    | No  | Yes   | Yes                       |
| Mixed <sup>d</sup>     | Yes   | Yes   | Yes                       |
| Undefined <sup>e</sup> | Yes   | No  | Yes                       |
|                        | Yes   | Yes   | No                        |

BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CT, computed tomography; FEV<sub>1</sub>, forced expiratory volume in 1 second; RAS, restrictive allograft syndrome; FVC, forced vital capacity; RAS, restrictive allograft syndrome; TLC, total lung capacity.

<sup>a</sup>Obstruction is defined by a fall in FEV<sub>1</sub> (as described in the text) and associated with other indices of airflow limitation (FEV<sub>1</sub>/FVC ratio <0.70).

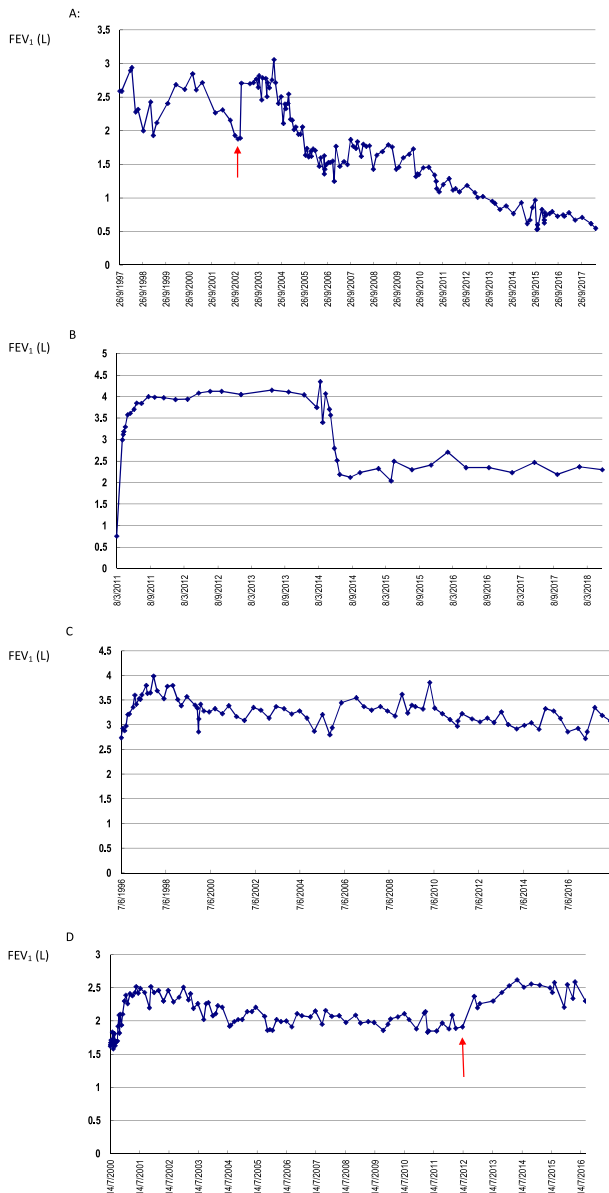
<sup>b</sup>Restriction is properly defined as a ≥10% reduction in baseline TLC.

<sup>c</sup>Refers to parenchymal opacities and/or increasing pleural thickening consistent with a diagnosis of pulmonary and/or pleural fibrosis and likely to cause a restrictive physiology, rather than the airway-based changes consistent with bronchiectasis. Although the 2 (opacities and bronchiectasis) may coexist, in some cases, the presence of bronchiectasis may reflect traction changes on airways due to fibrotic parenchymal opacities.

<sup>d</sup>By definition, all cases that transition from a BOS phenotype to an RAS phenotype and vice-versa, will meet these criteria, which is in accord with histopathologic findings at explant/post-mortem.

<sup>e</sup>Undefined means definite CLAD, but with 2 possible combinations of variables, making it difficult to categorize in the upper panels (BOS, RAS, or mixed phenotype).





**Figure 2** Case studies. (A) In 1997, this patient underwent a heart–lung transplant for complex Eisenmenger syndrome, and had several biopsy-proven acute cellular rejection episodes, which were treated with courses of intravenous steroids and intravenous anti-thymocyte globulins, and a shift from cyclosporine to tacrolimus and azathioprine to mycophenolate mofetil. Her FEV<sub>1</sub> decreased gradually from 2.92 liters to 1.88 liters, and she was diagnosed with CLAD Stage 2 (FEV<sub>1</sub> decline to 64% of baseline), phenotype BOS (obstructive and no CT opacities). At that time (in 2002), azithromycin was added (red arrow) and FEV<sub>1</sub> normalized within 2 months. CLAD could no longer be sustained, so it is unlikely that her FEV<sub>1</sub> decline before azithromycin was due to development of BO (BOS). Later, she had another gradual decline in FEV<sub>1</sub>, which was considered CLAD (initial BOS phenotype), but subsequently demonstrated a mixed phenotype with TLC decline (12%) and persistent pleuroparenchymal opacities on chest CT scan. (B) In 2011, this patient underwent a re-do bilateral lung transplant because of end-stage BOS. In 2014, after late biopsy-proven acute rejection, he developed rapidly declining obstructive spirometry, diagnosed as CLAD Stage 3, phenotype BOS. After initiation of extracorporeal photopheresis, FEV<sub>1</sub> increased from 2.12 liters to a maximum of 2.70 liters, after which it remained stable at around 2.35 liters. This patient showed partial reversibility

instance, FVC may be falsely reduced due to an increased residual volume (RV), rather pointing to obstruction. Also, after single-LTx for chronic obstructive pulmonary syndrome (COPD), or in the presence of anastomotic stenosis after bilateral LTx, the FEV<sub>1</sub>/FVC ratio may remain <0.7, even if RAS, and hence restriction develops. In that case, TLC decline may be the only indication for restriction in the pulmonary function testing. Another pitfall in the interpretation of the FEV<sub>1</sub>/FVC ratio is when the BOS phenotype moves into the mixed phenotype. In these patients, usually the FEV<sub>1</sub>/FVC ratio will also remain <0.7, but it may increase from the value at the last BOS spirometry. In that situation, development of persistent opacities on chest imaging and the associated decline in TLC of ≥10% may be the best indicators of a mixed phenotype development.

Chest CT may reveal opacities (ground glass, consolidation, small linear and reticular) that can be multilobar and/or show increasing pleural thickening consistent with a diagnosis of pulmonary and/or pleural fibrosis. This should be the probable cause of the restrictive physiology, rather than airway-based changes consistent with bronchiectasis, although the 2 may coexist, the latter, in some cases, reflecting traction changes on airways due to the former.

As a consequence, staging will be performed as follows: when a patient meets the criteria for CLAD, the CLAD stage will be attributed based on the percent FEV<sub>1</sub> decline, after which the phenotype will be mentioned based in the aforementioned criteria and Table 3. For example, 1 patient may have CLAD Stage 2 (FEV<sub>1</sub> >50% to 65%) with phenotype BOS (obstructive physiology, without radiologic opacities), whereas another patient may have CLAD Stage 1 (FEV<sub>1</sub> >65% to 80%), with phenotype RAS (TLC decline ≥10% and persistent opacities).

(+27%), with a subsequent new decline, although the patient has remained in CLAD Stage 2, phenotype BOS, illustrating that a reversible (possibly inflammatory) part of CLAD (BOS) was effectively treated, even though BO itself is not reversible. (C) In 1996, the patient underwent a bilateral lung transplantation for pulmonary arterial hypertension. The best post-operative FEV<sub>1</sub> was 3.9 liters (100% predicted). Current FEV<sub>1</sub> is 3.1 liters (98% predicted). Although there was an FEV<sub>1</sub> decline of 0.8 liter (corresponding to a 20.5% decline), this is not considered CLAD, as the percent predicted has remained almost identical; thus, this may be considered a natural FEV<sub>1</sub> decline over the course of 22 years. (D) In 2000, this patient underwent bilateral lung transplant for idiopathic pulmonary fibrosis. Her weight increased by 25 kg over the next 5 years, but then remained stable. At the same time, her FEV<sub>1</sub> and FVC decreased by 20% compared with baseline. This was initially considered CLAD Stage 1, with restrictive pulmonary function (TLC decline 11%), but there were no opacities on chest CT scan (hence not qualifying for RAS). After she underwent a gastric bypass procedure (red arrow), resulting in a weight loss of 30 kg, pulmonary function again normalized. The patient did not have CLAD because her restrictive pulmonary decline was due to weight gain, and CLAD score was restored to 0 with substantial weight loss. CLAD, chronic lung allograft dysfunction; CT, computerized tomography; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; RAS, restrictive allograft syndrome; TLC, total lung capacity.

Despite taking all of these parameters into consideration and making possible efforts to assign a phenotype, some patients may still be difficult to classify as having a specific phenotype. A patient with an obstructive defect who develops persistent opacities on HRCT but no decline in TLC or a patient with a combined obstructive and restrictive decline in pulmonary function without opacities on HRCT are representative examples of such a situation (see Table 3), which may represent a phenotype that has yet to be defined.

The underlying pathology of BOS is considered to be BO, which may be early, with an excess of sub-epithelial fibrous tissue, or late, with obliteration of the lumen by fibrosis. Remnants of smooth muscle may be identified in the scar of an obliterated bronchiole, and may be better demonstrated in the elastic lamina with an elastic van Gieson stain.

The pathology of RAS is commonly late-onset, diffuse alveolar damage progressing to end-stage pulmonary fibrosis with or without pleural involvement.<sup>5,19–22</sup> Post-mortem and explant analysis of lung tissue from patients with a restrictive defect commonly demonstrates BO as well as fibroelastosis (FE), which may be pleuroparenchymal (PPFE) or scattered in the lung parenchyma, and is qualitatively different from parenchymal fibrosis seen in non-transplant patients.<sup>19,21,22</sup> The concurrent finding of these 2 histopathologic changes in 1 biopsy sample can explain the finding of a combined obstructive and restrictive ventilatory defect and the potential evolution from one CLAD phenotype to another.

### Non-CLAD causes of pulmonary function decline

As defined earlier, CLAD represents a loss of lung function due to pathologic airway and parenchymal/pleural processes, encompassing BOS, RAS, mixed, and an (as-yet) undefined phenotype (Table 3). There are, however, a number of circumstances, comorbidities, and new-onset diseases that can also lead to a loss of lung function post-transplant, but these are *not* incorporated into the CLAD definition (Table 1).

Note that some of these processes may be stable and chronic (e.g., aging, lung or chest wall surgery, weight gain, and airway narrowing, as outlined in Table 1, section A). If these or other issues are identified, then the patient's "new" baseline FEV<sub>1</sub> should be redefined for future monitoring for any subsequent decline in lung function. The baseline FEV<sub>1</sub> should be reset when the underlying non-CLAD condition (Table 1, section A conditions only) has been stable for at least 6 months. In this 6-month period, the mean of 2 best FEV<sub>1</sub> measurements, taken at least 3 weeks apart, will be the new reference baseline FEV<sub>1</sub>.

Lung function will indeed change over time in the aging lung, which may confound the application of the CLAD criteria detailed previously. This situation can usually be resolved by analysis of whether there has been a significant change in the percentage of predicted lung function (Figure 2C). When graphed over time, a step change in slope is suggestive of the development of CLAD. Similarly,

the body habitus of the patient may change with increasing weight, leading to a restrictive pulmonary function (without any opacities on CXR/CT scan). Diagnosing CLAD may be difficult in these cases, except when there is subsequent weight loss with an improvement of pulmonary function (Figure 2D). Consideration should also be given to the donor-predicted values. This is particularly important when a donor/recipient sex mismatch occurs, when there is a large variance in age between the donor and recipient or between predicted lung sizes based on a height mismatch. Lungs from older smoking donors may also display some emphysematous changes, which will likely be reflected on the best FEV<sub>1</sub> achieved post-LTx. Once again, in each of these situations, a stable baseline is usually achieved within 3 to 6 months (rarely several years) of transplant, which can then be used to compute the reference values and the development of CLAD.

Other circumstances (as outlined in Table 1, section B) are unpredictable in the actual variability of extent (e.g., tumor- or drug-induced parenchymal infiltration), and both the presence of CLAD, as well as the timing of its onset, are difficult to clarify with accuracy.

### Tools for diagnosis of CLAD phenotype and suggested follow-up

The phenotype of CLAD is established using the diagnostic criteria outlined earlier (Table 3), and response to treatment is assessed predominantly by lung function and imaging. Patients with a first drop in FEV<sub>1</sub> of  $\geq 10\%$  should be investigated thoroughly and reassessed within 4 to 6 weeks, especially if a new treatment has been initiated. Spirometry (performed according to ATS/ERS standards) should be assessed at every clinic visit.<sup>23</sup> If bronchodilator response is performed, post-bronchodilator FEV<sub>1</sub> values should be used to exclude other (reversible) etiologies for obstruction. CLAD patients may stabilize their FEV<sub>1</sub> spontaneously or after treatment. In stable CLAD patients with stable FEV<sub>1</sub> or a very slow decline in FEV<sub>1</sub> (so-called plateau phase), it is advised to have lung function measured at least every 3 or 4 months. Home spirometry is a useful technique to detect early changes in graft function and to determine when to intervene.<sup>24</sup>

We recommend measuring TLC in LTx patients at 3 and 6 months after transplant and annually thereafter. TLC measurements should also be obtained if FEV<sub>1</sub> changes  $\geq 10\%$  from previous values. The "gold standard" technique to assess TLC is body plethysmography.<sup>25</sup>

The initial CT scans (inspiratory views with a maximum width of 3-mm sections, and expiratory sections as well) without contrast media are recommended in all LTx patients at 6-month follow-up (when spirometry is usually optimal). Repeat CT studies should be obtained when CLAD is initially diagnosed to better visualize air trapping and various subtle opacities. Dettmer et al recently demonstrated that a chest CT obtained at the onset of CLAD can predict the development of RAS as well as survival.<sup>26</sup> In addition, opacities on CXR that are not explained by

obvious causes (e.g., infection, drug toxicity, rejection, and malignancy) are indicators for a repeat chest CT. Multilobar opacities (ground glass, consolidation, small linear and reticular changes) that persist for 3 months with or without pleural changes are hallmark features of the RAS phenotype of CLAD.<sup>21</sup>

Transbronchial biopsy and bronchoalveolar lavage (BAL) have a major role in the detection of treatable causes prior to the diagnosis of definite CLAD and should be performed at the start of the diagnostic process to investigate the decline in lung function not explained by obvious, non-CLAD causes (Table 1). Once the diagnosis of CLAD has been established, these investigations have little role in follow-up of CLAD patients. There are no specific features that can be obtained from BAL, biopsy, or serum that are useful to phenotype CLAD. Rather, cytologic and microbiologic (including bacteria, viral and fungal) assessments of the BAL fluid should be obtained. Although transbronchial biopsy may detect an area of active or inactive BO, histopathologic evidence of BO is relatively uncommon, as the process is patchy and bronchial sampling is relatively limited. The detection of lymphocytic bronchiolitis after a diagnosis of CLAD is a poor prognostic indicator associated with decreased survival and the development of RAS<sup>27</sup> and BOS.<sup>28</sup>

Abnormalities seen on BAL cytology, such as when neutrophilia (>15%) or eosinophilia ( $\geq 2\%$ ) are present, have been associated with the development of CLAD.<sup>29,30</sup> In the absence of infection or colonization, persistent early BAL neutrophilia may signal the onset of BOS.<sup>29</sup> BAL eosinophilia that correlates with blood eosinophilia and raised C-reactive protein (CRP) has been associated with the development of RAS through unknown mechanisms. Peripheral blood eosinophilia is also associated with poor graft survival after the diagnosis of RAS.<sup>27</sup> BAL should also be assessed for signs of aspiration, which is suggested by the presence of multinucleated giant cells or foreign organic material (such as meat and plant material), and/or of lipid, as demonstrated on a lipid stain such as oil red-O or Sudan black and/or bile acids (detected by enzymatic assay).<sup>31</sup>

## Treatment of CLAD

There are few treatment options for CLAD and, to date, these have mostly been reported in patients with BOS and have shown limited efficacy. Effective pharmacologic therapy of CLAD remains an unmet medical need. Retransplantation may be the only therapeutic option for advanced CLAD in well-selected patients. However, retransplantation is associated with lower peak lung function as compared with a matched cohort of first transplant patients and carries a higher post-operative mortality, especially for RAS.<sup>32,33</sup>

In CLAD (BOS), sustained administration of high-dose corticosteroids should be avoided due to harmful side effects and lack of efficacy.<sup>5</sup> Other options include: conversion of cyclosporine to tacrolimus; a trial of azithromycin for  $\geq 8$  weeks; and fundoplication for documented gastroesophageal reflux in selected cases.<sup>5</sup> There are no formal treatment guidelines for RAS, and management is relatively

experimental, as no clinical studies have demonstrated the efficacy of any intervention.<sup>21</sup> However, some case reports and a small case series have demonstrated marginal effects (such as improvement or stabilization of interstitial changes and lung function) with off-label use of pirfenidone, nintedanib, or alemtuzumab.<sup>34–37</sup> Other therapeutic options for CLAD (BOS) include total lymphoid irradiation (TLI) or extracorporeal photopheresis (ECP).<sup>38–42</sup> TLI may reduce the rate of decline in graft function associated with BOS, which is mostly observed in "rapid decliners" (defined as those with an FEV<sub>1</sub> decline >100 ml/month pre-treatment).<sup>38,39</sup> Similar effects are seen with ECP, however, mostly in BOS patients with a slowly progressive FEV<sub>1</sub> decline and increased BAL neutrophilia. ECP is less likely to attenuate disease progression in rapidly declining BOS patients without significant BAL neutrophilia or in patients with RAS.<sup>40–43</sup>

Non-controlled studies in which azithromycin was added demonstrated an improvement and even normalization of the FEV<sub>1</sub> in a significant proportion of patients diagnosed with BOS and was typically associated with BAL neutrophilia.<sup>7,8,43–46</sup> A placebo-controlled, randomized trial published by Corris et al corroborated these results and also demonstrated that a treatment delay of several months did not have a negative impact on the improvement in FEV<sub>1</sub>.<sup>47</sup> Some beneficial effects with add-on montelukast have also been suggested in a small, open-label, pilot study and in a randomized, placebo-controlled, single center trial, although controversy of its effects remains.<sup>48,49</sup>

## Preventive treatment for CLAD

Although various allograft infections have been associated with CLAD onset and/or progression, randomized trials with anti-infective therapy as a primary preventive treatment for CLAD are lacking. However, interventions that target specific infections may reduce the prevalence of new-onset or progressive BOS, as was demonstrated in a randomized trial in LTx recipients with respiratory syncytial virus.<sup>50</sup> Similarly, sinus surgery and daily nasal care after LTx in cystic fibrosis patients has been advocated as a potential preventive measure for CLAD. Although such an approach may prevent aspiration of post-nasal secretions and reduce allograft infections and colonization, results from a recent randomized clinical trial did not demonstrate improved survival or a decreased incidence of CLAD.<sup>51</sup>

At present, only prophylactic treatment with azithromycin has been demonstrated to significantly reduce the prevalence of BOS in a randomized clinical trial.<sup>52,53</sup> Non-randomized studies have also suggested a reduced rate of BOS in LTx recipients receiving statins in comparison to non-treated patients, with a trend for a lower BOS prevalence in statin-treated patients and better maintenance of lung function after LTx.<sup>54,55</sup> A recent randomized, controlled trial with high-dose vitamin D did not demonstrate a decrease in BOS prevalence or improvement in BOS-free survival.<sup>56</sup> Two randomized, open-label clinical trials, one comparing mycophenolate sodium vs delayed-onset administration of

everolimus (both in combination with cyclosporine and corticosteroids) and the other comparing induction with alemtuzumab vs thymoglobulin, showed no difference in efficacy for prevention of BOS.<sup>57,58</sup> De-novo tacrolimus use, as compared with cyclosporine, was associated with a significantly reduced risk for BOS Grade  $\geq 1$  at 3 years after LTx, although the primary end-point was not assessed by independent data review.<sup>59</sup> Inhaled cyclosporine was reported to extend BOS-free survival compared with placebo in a small, randomized trial,<sup>60</sup> but these results were not supported in the CYCLIST trial.<sup>61</sup>

## Possible future treatments

A European multicenter, randomized, controlled Phase 3 trial with pirfenidone in BOS (NCT02262299) is currently ongoing (enrolling until mid-2019). Another study on the role of ECP for the management of progressive BOS (NCT02181257) is currently active.

Mesenchymal stromal cell therapy, shown to be safe and feasible,<sup>62</sup> is under investigation as a treatment for CLAD, and is currently being investigated in an Australian Phase 2, multicenter, randomized study (NCT02709343). In a retrospective analysis, Tikkanen et al suggested increased BOS-free survival when using normothermic ex-vivo lung perfusion (EVLP) in a comparison with contemporaneous cold preservation of lungs from brain-dead donors.<sup>63</sup> Long-term clinical results from a randomized trial with EVLP (INSPIRE) regarding pulmonary function and prevalence of CLAD are pending as of this writing.<sup>64</sup> Pre-emptive circulating antibody-directed treatment may mitigate the risk of later CLAD associated with human leukocyte antigen (HLA) donor-specific antibodies (DSA). However, evidence from placebo-controlled trials is needed to determine the efficacy of this approach.<sup>65</sup> Other non-medical interventions, such as supplemental oxygen or supervised pulmonary rehabilitation, may reduce CLAD-associated patient-reported complaints (dyspnea) or complications (deconditioning), but randomized data with which to base firm recommendations on symptomatic treatments are lacking.<sup>5</sup> Mobile health interventions may also be associated with reduced risk of BOS, most likely by facilitating improved self-management and compliance with complex post-transplant medical regimens.<sup>66</sup>

## Limitations and future directions

The definitions introduced in this report are limited to the consensus opinions of experts in LTx and thus lack the "hard data" to support individual statements. Consequently, there remains significant subjectivity in the CLAD definition, and the astute clinician must take this into account. Specific limitations are outlined in what follows.

### Limitations

*Subjectivity in the CLAD definition.* CLAD remains a clinical diagnosis. In spite of the definitions given in this

consensus report, subjectivity in the exact classification of patients, as well as timing of onset of CLAD, cannot be eliminated. These caveats must be incorporated into the design of future research studies and the assessment of published literature on the subject.

The CLAD definition itself, which is based on a sustained  $\geq 20\%$  drop in FEV<sub>1</sub> compared with baseline, is a relatively objective approach to the diagnosis, but the threshold is perforce arbitrary. The exclusion of other diagnoses is more nuanced. In some cases, CLAD may occur concurrently with other complications, such as pleural effusion, diaphragmatic dysfunction, weight gain, and other causes, as discussed earlier. Therefore, the essential question is whether the decrease in FEV<sub>1</sub> is due to CLAD or to a concurrent disease/disorder (or both), which is often a subjective decision. Another question is whether the post-transplant FEV<sub>1</sub> baseline should be reset after certain diseases or processes have been identified that permanently affect lung function and are not directly related to allograft complications (such as a lobectomy or weight gain) (Table 1, section A). In these settings, a diagnosis of CLAD should be based on the new FEV<sub>1</sub> baseline value, as described earlier. Such considerations should be made on a case-by-case basis, but such instances relatively rare. However, the baseline should not be reset after conditions that are known risk factors for CLAD (such as acute cellular or antibody-mediated rejection, and infection), as these often cause a stepwise decline in FEV<sub>1</sub> in the progression of graft dysfunction to CLAD.

The timing of CLAD onset is an important discussion point, particularly as it is greatly influenced by the frequency of pulmonary function testing (PFT). We recommend PFT values used for assessment should be consistently obtained at a single, accredited PFT laboratory to assure that the values measured are compared with standardized equations not utilized at smaller PFT laboratories. Similarly, home spirometry devices may provide more variable results as they are not calibrated on a routine basis. These factors should be taken into account when comparing data from different centers. A good consensus on timing of CLAD onset is imperative and definitions must be standardized to facilitate the objectivity in uniformity for enrollment criteria and outcome measures in clinical trials.

This consensus report thus has defined that CLAD onset occurs at the time of measurement of the first decline in FEV<sub>1</sub>  $\geq 20\%$  from baseline. This differs from previously used criteria that excluded data showing initial FEV<sub>1</sub>  $\leq 80\%$  of baseline if associated with rejection or infection, and rather, CLAD was declared if FEV<sub>1</sub> remained suppressed yet active rejection or infection were excluded. These criteria are considered by this group to be too subjective and highly dependent on the frequency of surveillance tests such as spirometry, body plethysmography, bronchoscopy, biopsy, and other diagnostic tests. Thus, the criteria to determine the presence of CLAD is failure of FEV<sub>1</sub> to improve to  $>80\%$  of baseline after adequate treatment of infection or rejection, and the start of CLAD is noted at the first test to demonstrate a decrease in the FEV<sub>1</sub>  $\geq 20\%$  from baseline.



We acknowledge that the  $\geq 20\%$  decline in FEV<sub>1</sub> is somewhat arbitrary. Specific quantification is relevant and probably should be reassessed in the modern era in the context of RAS and BOS definitions.

Defining CLAD in the absence of PFT remains a difficult issue. Some patients have clear (acute-onset) lung allograft dysfunction but are too sick to have spirometry. Our consensus group has determined that the term CLAD should not be employed in these instances. In some patients, radiologic evidence (air trapping, bronchiectasis, pleuroparenchymal opacities) or pathologic evidence (BO, pleuroparenchymal fibroelastosis) of CLAD is noted, yet serial spirometric data have not been collected. More precise definitions need to be developed for these CLAD-like clinical entities.

At this time, CLAD is defined as the presence of an irreversible or partly reversible (to  $\leq 80\%$  of baseline) FEV<sub>1</sub> change upon treatment. However, the definition will need to be revised if more effective therapies for CLAD are introduced that reverse the disease process to within  $>80\%$  of baseline.

This report has focused on the 3 phenotypes (BOS, RAS, and the mixed phenotype) described to date. However, other phenotypes may exist, based on a different combination of lung function variables and other clinical features (undefined, see Table 3). Ultimately, endotypes will likely be developed that are based on biologic variables rather than clinical phenotypes. The field continues to evolve as clinicians strive to determine which classifications are most relevant to prognosis, early diagnosis, and response to treatment.

## Future directions

Future research and discussions regarding CLAD diagnosis should focus on:

- Better characterization of other (undefined) phenotypes of CLAD.
- Better definition of post-transplant predicted lung function values.
- Use of other pulmonary function tests to characterize CLAD subtypes, such as forced expiratory flow and diffusing capacity for carbon monoxide (DLCO).
- Quantitative assessment of chest CT opacities.
- Magnetic resonance imaging (MRI) allowing serial assessments of ventilation and opacities without radiation exposure and contrast media.<sup>67</sup>
- Better descriptions of CLAD-like entities that do not fit the definition, such as:
  1. Failure to achieve adequate lung function. Indeed, underlying processes may affect baseline lung function immediately after LTx, with the recipient achieving a very low maximal FEV<sub>1</sub>. Multiple factors may contribute to this inability to achieve an adequate lung function, but this does not change the approach to CLAD diagnosis, although it has an impact on survival.<sup>68</sup>
  2. Allograft dysfunction in the absence of PFT data.
  3. Overlap processes.

In summary, in this report we have aimed to further unify the CLAD-specific language within the LTx community with the aim of improving our understanding of CLAD mechanisms and allowing for standardized measurements within multicenter studies and clinical trials that aim to develop effective therapies.

The path toward these goals can be summarized in the following 3 categories:

1. Improving graft surveillance for early detection of CLAD: Patterns of spirometric and/or volumetric changes over time, combined with quantitative measurements of radiographic findings and biologic markers will allow a more comprehensive longitudinal monitoring of LTx recipients.
2. From physiologic phenotyping to biologic endotyping: Recent data have identified many biomarkers of CLAD, RAS, and BOS that affect survival. These markers include BAL proteins and RNA transcripts, lung tissue RNA transcripts, and allograft-derived cell analyses.<sup>5,69–74</sup> Biologic markers such as these can be evaluated to define endotypes of CLAD that reflect the underlying pathology of the disease process. Characterizing CLAD patients based on up- or downregulated biologic processes may help better predict responsiveness to specific therapies in the future. There are no biomarkers that specifically identify any single CLAD phenotype. Studies in this area are currently in progress.
3. Tailoring of therapeutic modalities: More effective personalized immunomodulatory therapies as well as anti-fibrotic approaches are greatly needed in LTx. Better understanding of CLAD phenotypes and endotypes will help in the development and selection of such therapeutics.
4. Clear definitions of CLAD phenotypes, as described in this consensus report, will help us harmonize patient recruitment for multicenter studies.

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## References

1. Opelz G, Döhler B, Ruhstroth A, et al. The Collaborative Transplant Study Registry. *Transplant Rev* 2013;27:43-5.
2. Chambers DC, Yusef RD, Cherikh WS, et al. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult lung and heart–lung transplantation report—2017; Focus theme: Allograft ischemic time. *J Heart Lung Transplant* 2017;36:1047-59.

3. Cooper JD, Billingham M, Egan T, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. *J Heart Lung Transplant* 1993;12:713-6.
4. Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 2002;21:297-310.
5. Meyer KC, Raghu G, Verleden GM, et al. ISHLT/ATS/ERS BOS Task Force Committee; ISHLT/ATS/ERS BOS Task Force Committee. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. *Eur Respir J* 2014;44:1479-503.
6. Palmer SM, Miralles AP, Howell DN, Brazer SR, Tapson VF, Davis RD. Gastroesophageal reflux as a reversible cause of allograft dysfunction after lung transplantation. *Chest* 2000;118:1214-7.
7. Gerhardt SG, McDyer JF, Giris RE, Conte JV, Yang SC, Orens JB. Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: results of a pilot study. *Am J Respir Crit Care Med* 2003;168:121-5.
8. Verleden GM, Dupont LJ. Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2004;77:1465-7.
9. Pakhale SS, Hadjiliadis D, Howell DN, et al. Upper lobe fibrosis: a novel manifestation of chronic allograft dysfunction in lung transplantation. *J Heart Lung Transplant* 2005;24:1260-8.
10. Sato M, Waddell TK, Wagnetz U, et al. Restrictive allograft syndrome (RAS): a novel form of chronic lung allograft dysfunction. *J Heart Lung Transplant* 2011;30:735-42.
11. Glanville AR. Bronchoscopic monitoring after lung transplantation. *Semin Respir Crit Care Med* 2010;31:208-21.
12. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant* 2014;33:127-33.
13. Glanville AR. CLAD: does the emperor have new clothes? *Am J Transplant* 2014;14:2681-2.
14. Kapila A, Baz MA, Valentine VG, et al. Reliability of diagnostic criteria for bronchiolitis obliterans syndrome after lung transplantation: a survey. *J Heart Lung Transplant* 2015;34:65-74.
15. 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 Transplant* 2016;35:397-406.
16. Glanville AR. Physiology of chronic lung allograft dysfunction: back to the future? *Eur Respir J* 2017;49(4).
17. Sato M, Hwang DM, Waddell TK, Singer LG, Keshavjee S. Progression pattern of restrictive allograft syndrome after lung transplantation. *J Heart Lung Transplant* 2013;32:23-30.
18. Verleden GM, Vos R, Verleden SE, et al. Survival determinants in lung transplant patients with chronic allograft dysfunction. *Transplantation* 2011;92:703-8.
19. Sato M, Hwang DM, Ohmori-Matsuda K, et al. Revisiting the pathological finding of diffuse alveolar damage after lung transplantation. *J Heart Lung Transplant* 2012;31:354-63.
20. Todd JL, Jain R, Pavlisko EN, et al. Impact of forced vital capacity loss on survival after the onset of chronic lung allograft dysfunction. *Am J Respir Crit Care Med* 2014;189:159-66.
21. Glanville AR, Verleden GM, Todd J, 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 Transplant* 2019;38:483-92.
22. Ofek E, Sato M, Saito T, et al. Restrictive allograft syndrome post lung transplantation is characterized by pleuroparenchymal fibroelastosis. *Mod Pathol* 2013;26:350-6.
23. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
24. de Wall C, Dettmer S, Warnecke G, et al. Home spirometry as early detector of azithromycin refractory bronchiolitis obliterans syndrome in lung transplant recipients. *Respir Med* 2014;108:405-12.
25. Garfield JL, Marchetti N, Gaughan JP, Steiner RM, Criner GJ. Total lung capacity by plethysmography and high-resolution computed tomography in COPD. *Int J Chron Obstruct Pulmon Dis* 2012;7:119-2.
26. Dettmer S, Shin H, Vogel-Claussen J, et al. CT at onset of chronic lung allograft dysfunction in lung transplant patients predicts development of the restrictive phenotype and survival. *Eur J Radiol* 2017;94:78-84.
27. Verleden SE, Ruttens D, Vandermeulen E, et al. Predictors of survival in restrictive chronic lung allograft dysfunction after lung transplantation. *J Heart Lung Transplant* 2016;35:1078-84.
28. Greenland JR, Jones KD, Hays SR, et al. Association of large-airway lymphocytic bronchitis with bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2013;187:417-23.
29. Neurohr C, Huppmann P, Samweber B, et al. Prognostic value of bronchoalveolar lavage neutrophilia in stable lung transplant recipients. *J Heart Lung Transplant* 2009;28:468-74.
30. Verleden SE, Ruttens D, Vandermeulen E, et al. Elevated bronchoalveolar lavage eosinophilia correlates with poor outcome after lung transplantation. *Transplantation* 2014;97:83-9.
31. Mertens V, Blondeau K, Van Oudenhove L, et al. Bile acids aspiration reduces survival in lung transplant recipients with BOS despite azithromycin. *Am J Transplant* 2011;11:329-35.
32. Verleden SE, Todd JL, Sato M, et al. Impact of CLAD phenotype on survival after lung retransplantation: a multicenter study. *Am J Transplant* 2015;15:2223-30.
33. Halloran K, Aversa M, Tinkam K, et al. Comprehensive outcomes after lung retransplantation: a single-center review. *Clin Transplant* 2018;32:e13281.
34. Vos R, Verleden SE, Ruttens D, et al. Pirfenidone: a potential new therapy for restrictive allograft syndrome? *Am J Transplant* 2013;13:3035-40.
35. Vos R, Wuyts WA, Gheysens O, et al. Pirfenidone in restrictive allograft syndrome after lung transplantation: a case series. *Am J Transplant* 2018;18:3045-59.
36. Suhling H, Bollmann B, Gottlieb J. Nintedanib in restrictive chronic lung allograft dysfunction after lung transplantation. *J Heart Lung Transplant* 2016;35:939-40.
37. Kohno M, Perch M, Andersen E, Carlsen J, Andersen CB, Iversen M. Treatment of intractable interstitial lung injury with alemtuzumab after lung transplantation. *Transplant Proc* 2011;43:1868-70.
38. Fisher AJ, Rutherford RM, Bozzino J, Parry G, Dark JH, Corris PA. The safety and efficacy of total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation. *Am J Transplant* 2005;5:537-43.
39. Verleden GM, Lievens Y, Dupont LJ, et al. Efficacy of total lymphoid irradiation in azithromycin nonresponsive chronic allograft rejection after lung transplantation. *Transplant Proc* 2009;41:1816-20.
40. Benden C, Haughton M, Leonard S, Huber LC. Therapy options for chronic lung allograft dysfunction—bronchiolitis obliterans syndrome following first-line immunosuppressive strategies: a systematic review. *J Heart Lung Transplant* 2017;36:921-33.
41. Yung GL, Craig V. Lung transplantation and extracorporeal photopheresis: the answer to bronchiolitis obliterans? *Transfus Apher Sci* 2015;52:162-6.
42. Greer M, Dierich M, De Wall C, et al. Phenotyping established chronic lung allograft dysfunction predicts extracorporeal photopheresis response in lung transplant patients. *Am J Transplant* 2013;13:911-8.
43. Yates B, Murphy DM, Forrest IA, et al. Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2005;172:772-5.
44. Gottlieb J, Szangolies J, Koehnlein T, Golpon H, Simon A, Welte T. Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. *Transplantation* 2008;85:36-41.
45. Jain R, Hachem RR, Morrell MR, et al. Azithromycin is associated with increased survival in lung transplant recipients with bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2010;29:531-7.
46. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE. Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. *Am J Respir Crit Care Med* 2006;174:566-70.
47. Corris PA, Ryan VA, Small T, et al. A randomised controlled trial of azithromycin therapy in bronchiolitis obliterans syndrome (BOS) post lung transplantation. *Thorax* 2015;70:442-50.

48. Verleden GM, Verleden SE, Vos R, et al. Montelukast for bronchiolitis obliterans syndrome after lung transplantation: a pilot study. *Transpl Int* 2011;24:651-6.
49. Ruttens D, Verleden SE, Demeyer H, et al. A proof of concept: addition of montelukast compared to placebo for bronchiolitis obliterans syndrome after lung transplantation. *PLoS One* 2018; 13:e0193564.
50. Gottlieb J, Zamora MR, Hodges T, et al. ALN-RSV01 for prevention of bronchiolitis obliterans syndrome after respiratory syncytial virus infection in lung transplant recipients. *J Heart Lung Transplant* 2016; 35:213-21.
51. Vital D, Hofer M, Benden C, et al. Impact of sinus surgery on pseudo-monial airway colonization, bronchiolitis obliterans syndrome and survival in cystic fibrosis lung transplant recipients. *Respiration* 2013;86:25-31.
52. Vos R, Vanaudenaerde BM, Verleden SE, et al. A randomised controlled trial of azithromycin to prevent chronic rejection after lung transplantation. *Eur Respir J* 2011;37:164-72.
53. Ruttens D, Verleden SE, Vandermeulen E, et al. Prophylactic azithromycin therapy after lung transplantation: post hoc analysis of a randomized controlled trial. *Am J Transplant* 2016;16:254-61.
54. Johnson BA, Iacono AT, Zeevi A, et al. Statin use is associated with improved function and survival of lung allografts. *Am J Respir Crit Care Med* 2003;167:1271-8.
55. Li Y, Gottlieb J, Ma D, et al. Graft-protective effects of the HMG-CoA reductase inhibitor pravastatin after lung transplantation—a propensity score analysis with 23 years of follow-up. *Transplantation* 2011;92: 486-92.
56. Vos R, Ruttens D, Verleden SE, et al. High-dose vitamin D after lung transplantation: a randomized trial. *J Heart Lung Transplant* 2017;36: 897-905.
57. Glanville AR, Aboyoun C, Klepetko W, et al. Three-year results of an investigator-driven multicenter, international, randomized open-label de novo trial to prevent BOS after lung transplantation. *J Heart Lung Transplant* 2015;34:16-25.
58. Jaksch P, Ankersmit J, Scheed A, et al. Alemtuzumab in lung transplantation: an open-label, randomized, prospective single center study. *Am J Transplant* 2014;14:1839-45.
59. Treede H, Glanville AR, Klepetko W, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. *J Heart Lung Transplant* 2012;31: 797-804.
60. Iacono AT, Johnson BA, Grgurich WF, et al. A randomized trial of inhaled cyclosporine in lung-transplant recipients. *N Engl J Med* 2006; 12(354):141-50.
61. Johnson BA, Zamora MR, Budev MM, et al. Cyclosporine inhalation solution does not improve bronchiolitis obliterans syndrome-free survival following lung transplant: results from the CYCLIST trial. *J Heart Lung Transplant* 2012;31(suppl):S66.
62. Chambers DC, Enever D, Lawrence S, et al. Mesenchymal stromal cell therapy for chronic lung allograft dysfunction: results of a first-in-man study. *Stem Cells Transl Med* 2017;6:1152-7.
63. Tikkanen JM, Cypel M, Machuca TN, et al. Functional outcomes and quality of life after normothermic ex vivo lung perfusion lung transplantation. *J Heart Lung Transplant* 2015;34:547-56.
64. Warnecke G, Van Raemdonck D, Smith MA, et al. Normothermic ex vivo preservation with the portable Organ Care System Lung device for bilateral lung transplantation (INSPIRE): a randomised, open-label, non-inferiority, phase 3 study. *Lancet Respir Med* 2018;6:357-67.
65. Hachem RR, Yusen RD, Meyers BF, et al. Anti-human leukocyte antigen antibodies and preemptive antibody-directed therapy after lung transplantation. *J Heart Lung Transplant* 2010;29:973-80.
66. Rosenberger EM, DeVito Dabbs AJ, DiMartini AF, et al. Long-term follow-up of a randomized controlled trial evaluating a mobile health intervention for self-management in lung transplant recipients. *Am J Transplant* 2017;17:1286-93.
67. Voskrebenezov A, Greer M, Gutberlet M, et al. Detection of chronic lung allograft dysfunction using ventilation-weighted Fourier decomposition MRI. *Am J Transplant*, in press.
68. Liu J, Jackson K, Weinkauff J, et al. Baseline lung allograft dysfunction is associated with impaired survival after double-lung transplantation. *J Heart Lung Transplant* 2018;37:895-902.
69. Verleden SE, Gottlieb J, Dubbeldam A, et al. “White-out” after lung transplantation: a multicenter cohort description of late acute graft failure. *Am J Transplant* 2017;17:1905-11.
70. Jonigk D, Rath B, Borchert P, et al. Comparative analysis of morphological and molecular motifs in bronchiolitis obliterans and alveolar fibroelastosis after lung and stem cell transplantation. *J Pathol Clin Res* 2017;3:17-28.
71. Berastegui C, Gómez-Ollés S, Sánchez-Vidaurre S, et al. BALF cytokines in different phenotypes of chronic lung allograft dysfunction in lung transplant patients. *Clin Transplant* 2017;31(3).
72. Saito T, Liu M, Binnie M, et al. Distinct expression patterns of alveolar “alarmins” in subtypes of chronic lung allograft dysfunction. *Am J Transplant* 2014;14:1425-32.
73. Saito T, Liu M, Binnie M, et al. Upregulation of alveolar neutrophil enzymes and long pentraxin-3 in human chronic lung allograft dysfunction subtypes. *J Thorac Cardiovasc Surg* 2018;155:2774-6.
74. Verleden SE, Ruttens D, Vos R, et al. Differential cytokine, chemokine and growth factor expression in phenotypes of chronic lung allograft dysfunction. *Transplantation* 2015;99:86-93.