Chronic lung allograft dysfunction after lung transplantation: prevention, diagnosis and treatment in 44 European centres

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Shareable abstract (@ERSpublications)
This study describes real-world experience in Europe regarding CLAD management. The dataset represents 62% of European lung transplant centres. CLAD prevalence can be estimated to be 9 cases per million population in Europe. https://bit.ly/3Z3dwb3

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Abstract

Background There are limited data on optimal management of chronic lung allograft dysfunction (CLAD). We aimed to describe the variability of diagnostic and therapeutic practices in Europe.

Methods A structured questionnaire was sent to 71 centres in 24 countries. Questions were related to contemporary clinical practices for workup, monitoring and treatment of CLAD. The number of lung transplant procedures and patients in follow-up were collected.

Results 44 centres (62%) responded from 20 countries, representing 74% of European activity. The prevalence of CLAD was estimated at 9.1 cases per million population (25th and 75th percentiles of 4.4, 15.7). Preferred initial workup for probable CLAD consisted of chest computed tomography (CT) (inspiratory 91% and expiratory 74%), donor-specific antibody (DSA) measurement (86%), bronchoalveolar lavage (BAL) (85%) and transbronchial biopsy (81%). For monitoring of definite CLAD, inspiratory CT (67%), DSA (61%) and BAL (43%) were preferred. Body plethysmography was unavailable for 16% of cases. Prophylaxis was based on preventing infections (cytomegalovirus 99%, inhaled antibiotics 70% and antifungals 65%), tacrolimus-based immunosuppression (96%), azithromycin (72%) and universal proton pump inhibitor treatment (84%). First-line treatment of CLAD was based on azithromycin (82%) and steroid augmentation (74%). Photopheresis was used in 26% of cases.

Conclusion Current European practice CLAD detection is based on spirometry, inspiratory CT and DSA, with limited access to plethysmography and expiratory CT. Prophylactic treatment is based on azithromycin, tacrolimus-based immunosuppression and treatment of risk factors. No single treatment strategy is universally used, highlighting the need for an effective treatment of CLAD. The preferred first-line strategy is azithromycin and steroid augmentation.

Lessons for clinicians

- There are no data on current clinical practice on how CLAD is diagnosed, prevented or treated in Europe.
- This study describes, for the first time, real-world experience, the variability in diagnostic and therapeutic practices between lung transplant centres in Europe regarding CLAD management. The dataset represents 62% of European lung transplant centres. CLAD prevalence can be estimated to be 9 cases per million population in Europe, highlighting CLAD as a rare disease.
- Understanding the reality of current daily practice is a first step in designing feasible research projects to improve the detection, prevention and treatment of CLAD, aimed at improving post-transplant patient outcomes.

Introduction

Chronic lung allograft rejection (CLAD) is the major obstacle to improve long-term outcomes after lung transplantation (LTx). It is a major cause of morbidity and the leading cause of mortality after LTx, affecting up to 50% of patients after 5 years [1]. CLAD is defined by a persistent and usually progressive decline in forced expiratory volume in 1 s (FEV_1) [2] and is a diagnosis of exclusion of other causes of allograft dysfunction. The disease includes two main phenotypes: bronchiolitis obliterans syndrome (BOS), which typically manifests as airflow limitation due to fibrotic obliteration of the small airways, and restrictive allograft syndrome (RAS), which presents with progressive lung restriction and alveolar fibrosis. The pathophysiology of CLAD remains poorly understood. The heterogeneity of CLAD presentation and variable natural history poses a challenge in predicting outcomes and tailoring individualised treatment approaches.

Diagnostic tools such as pulmonary function tests and imaging modalities such as computed tomography (CT) are recommended for diagnosing, phenotyping and monitoring CLAD, and invasive procedures such as transbronchial biopsy are used to rule out other diseases. There is no effective medical treatment for CLAD, so prevention is a cornerstone of management. There is a lack of positive results from the available small randomised controlled trials for the treatment of CLAD patients [3, 4]. Once optimisation of immunosuppressive therapy is performed and responsiveness to steroids and azithromycin have been ruled out, options such as lymphocyte-depleting therapies, immunomodulatory treatments (*e.g.* photopheresis), supportive care and, in selected cases, re-transplantation can be discussed. Clinical experience suggests variability in its management and the optimal management strategy for CLAD is not well defined, with limited evidence to guide diagnostic and therapeutic decisions.

Addressing these knowledge gaps is critical to improving outcomes for LTx recipients at risk or affected by CLAD. This study aims to describe the variability in diagnostic and therapeutic practices among LTx centres in Europe to understand the reality of current daily practice, as a first step towards designing feasible research projects to improve the prevention, detection and treatment of CLAD, aimed at improving post-transplant patient outcomes.

Methods

A survey research study was conducted and initiated by the European Reference Network of Rare Lung Diseases (ERN-LUNG). ERN-LUNG is a patient-centric network of European healthcare providers and patient organisations, committed Europe-wide and globally to reducing morbidity and mortality from rare lung diseases through patient care, advocacy, education, research and knowledge-sharing. A questionnaire (see supplementary information) of 58 questions was developed by the ERN-CLAD working group members. A link to the online questionnaire (SoSci Survey GmbH, Munich, Germany) was sent to 71 centres in 24 European countries on 19 January 2024. Questions were targeted either for all currently used options used to diagnose and monitor CLAD patients or to prevent CLAD (prophylaxis) in *de novo* patients or to treat patients with proven CLAD (see survey in supplementary information). The question specifically asked about the percentage of patients treated with each option and multiple options could be given.

Names and addresses of centre representatives were identified by personal contact within the ERN-CLAD steering group. Reminders were sent by e-mail on 31 January and 26 February 2024. A single filled-out questionnaire from each centre was used for analysis. National transplant activity was extracted from the European Directorate for the Quality of Medicines & Health Care and centre activity from Eurotransplant and centre reports.

CLAD was defined as a persistent decline of FEV_1 of $\geqslant$20% of baseline as previously described in European LTx research projects [5, 6].

The study was performed according to the 1975 Declaration of Helsinki and the standards of the 2008 Declaration of Istanbul. The Ethics Committee at the Hannover Medical School approved the study protocol (11345_BO_S_2024). The dataset did not contain any personal patient data and informed consent was waived according to standard policies. No funding was received.

For statistical analysis, metric variables were expressed as medians and 25th and 75th quartiles and categorical variables were expressed as absolute numbers and percentages of data entries. The percentage of options used in the answers was multiplied by the number of active CLAD patients in follow-up (*e.g.* 50% of option A in 250 active CLAD patients in follow-up at centre X=125 patients used option A in centre X) for the categories workup, monitoring and treatment of CLAD. For prophylaxis of CLAD, all patients in active follow-up were used accordingly. For each option within a category (workup, monitoring, prevention and treatment) the total number of patients in whom the option was used, not used or unavailable was calculated. The percentages for each option were calculated by dividing by the total number of patients.

For additional options mentioned in the comments, 100% of patients in that centre were assumed to use this option except if otherwise specified in the comments. Additional treatment options were calculated to be used in 100% of patients if mentioned in the first line of therapy, in 50% of patients if mentioned in the second line and in 25% of patients if used on the third line or higher.

Data were analysed as observed without imputation of missing values.

Results

Of the 71 European centres contacted, 44 (62%) responded and completed the online questionnaire. The final dataset contained responses from 20 different countries. Out of the contacted national centres, responses from Estonia, Greece, Portugal and Turkey were missing. Centre demographics are displayed in table 1. Nine centres (20%) were high-volume centres reporting more than 50 LTx annually within the last 5 years and 14 (32%) performed fewer than 20 LTx procedures per year. In total, 13 417 patients were actively followed after LTx, and 3753 (28%) of patients in follow-up were affected by CLAD. The prevalence of CLAD was estimated at 9.1 cases per million population (pmp; 25% and 75% percentiles 4.4, 15.7) among the reporting countries.

The total annual LTx activity of centres from 20 responding countries was 1482. In relation to the reported 2022 annual activity reported by the Council of Europe (n=1992) [7], this activity represents 74% of the European LTx activity (table 1).

Completeness regarding the use of different options was excellent. Options to diagnose potential CLAD at onset were answered in 98%, for follow-up monitoring of CLAD patients in 95%, for CLAD prevention in 99% and for CLAD therapy in 98%.

TABLE 1 Centre characteristics (n=44)

Annual lung transplant activity per centre	30 (17, 45)
Total lung transplant activity[#]	1479 (74)
Countries[#]	**n=20**
Austria	1 (94)
Belgium	3 (96)
Croatia	1 (100)
Czech Republic	1 (100)
Denmark	1 (100)
Finland	1 (100)
France	5 (62)
Germany	8 (95)
Hungary	1 (100)
Ireland	1 (100)
Italy	4 (60)
Latvia	1 (100)
Netherlands	2 (59)
Norway	1 (100)
Poland	1 (28)
Slovenia	1 (100)
Spain	4 (57)
Sweden	2 (100)
Switzerland	1 (57)
Ukraine	1 (100)
United Kingdom	3 (90)
Annual re-do lung transplant activity per centre	1 (0, 2)
LTx patients in active follow-up per centre	250 (137, 400)
LTx patients with CLAD in active follow-up per centre	55 (25, 150)
Proportion of LTx patients with CLAD in active follow-up	23 (14, 36)

Data are presented as n (%) or median (25th, 75th percentile). LTx: lung transplantation; CLAD: chronic lung allograft dysfunction. [#]: % of European annual activity.

Spirometry was presumed essential for the workup and monitoring of CLAD cases. CT was most frequently used, with inspiratory scans performed in 91% and expiratory scans in 74% of patients (figure 1). Bronchoscopy was used in the majority of cases with bronchoalveolar lavage (BAL) and transbronchial biopsy (TBB) being the most frequently used sampling techniques. Concerning blood tests, analysis of donor-specific antibodies (DSA) was used in 86% of patients. In addition to the selectable options, arterial blood gases were checked in 7% of patients and donor-derived cell-free DNA in 5%, as noted in the comments. Further mentioned tests were the sit-to-stand test (1% of patients), ventilation-perfusion scintigraphy (1%) and the electronic nose (1%).

For monitoring of patients with definite CLAD, CT scans and bronchoscopic sampling were most frequently used in 8–43% of patients (figure 2). Body plethysmography, diffusion capacity and quality of life assessment were unavailable in 16%, 22% and 36% of CLAD patients, respectively.

For the prevention of CLAD in *de novo* patients, cytomegalovirus (CMV) prophylaxis was used almost universally in patients at risk (figure 3). Tacrolimus-based immunosuppression was used in 96% of cases, mycophenolate-based immunosuppression in 33% of cases and a universal proton pump inhibitor (PPI) in 84% of all patients after LTx. Reflux surgery (fundoplication) was performed only in 19% of patients with gastro-oesophageal reflux disease (GERD). Other options mentioned as a comment were inhaled corticosteroids in 8% and induction therapy to prevent CLAD in 7% of patients.

For treatment of CLAD patients, a minimum 4-week trial of azithromycin was used in 82% (figure 4). Some form of steroid therapy was used in the majority of patients: 47% by intravenous pulse and 27% by increased oral dose (figure 4). Inhaled bronchodilators were used in 38% of patients and best supportive care in 35%. Photopheresis was used in 26% of cases. In 7% of cases, re-transplantation was discussed; the annual re-do transplants accounted for a median of 4% of the total activity of the participating centres.

Concerning the sequence of first-line CLAD therapy (table 2), optimisation of maintenance immunosuppressive treatment, azithromycin and increased steroids were the main options used.

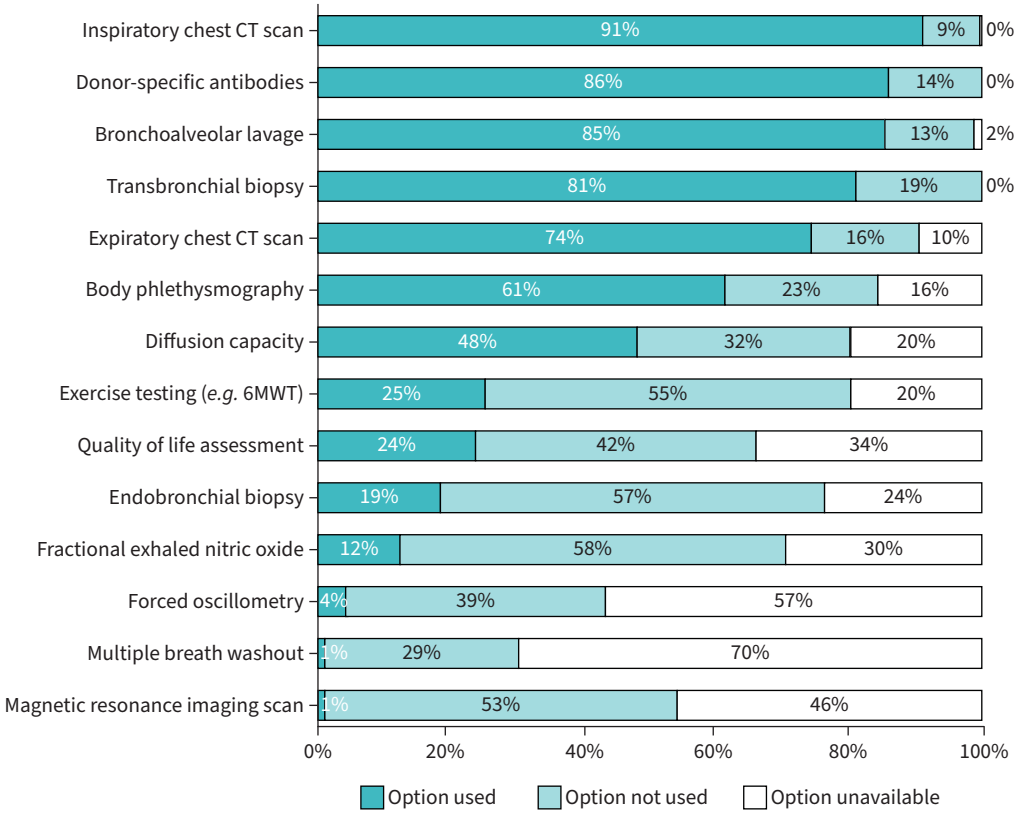

FIGURE 1 Diagnostic tests for evaluation of possible chronic lung allograft dysfunction (CLAD) patients (n=44 centres). CT: computed tomography; 6MWT: 6-min walk test.

Discussion

This is the first paper to describe the real-world CLAD landscape in Europe, capturing the detection, prevention and treatment of this complication and representing 74% of European LTx activity. In addition, our data give a prevalence of the disease in Europe of around nine cases pmp, highlighting CLAD as a rare disease.

The results from the survey in terms of CLAD detection agree with the International Society of Heart and Lung Transplantation (ISHLT) guidelines [4], which propose the definition of CLAD on spirometry parameters (mainly FEV_1) but recommends CT scan, BAL and TBB to detect treatable causes before the diagnosis of definite CLAD at the beginning of the diagnostic process. Other recommended tests such as expiratory chest CT scan and body plethysmography were not performed in 16% and 39% of our cohort, respectively. Both tests are necessary to phenotype CLAD but different factors might impact its use (unstable clinical situation, impossibility to perform during the pandemic, *etc.*). Expiratory CT scans can be more sensitive for detecting small airway disease early and specifically BOS [5, 6]. Surprisingly, this simple test was unavailable in 10% of cases. Similarly, body plethysmography was not available in 16% of cases and was not used in 23% of cases, although total lung capacity is essential for CLAD phenotyping. Due to the noninvasive nature of these tests and very limited contraindications, centres should be encouraged to use these options in patients with probable CLAD and during the evolution of the disease.

Although few studies describe the utility of forced oscillometry [8, 9], magnetic resonance imaging [10] or multiple breath washout [11] these tests have not made it yet to the general clinical practice. This finding is confirmed by our survey results with use in up to 12% of these methods. Overall, European centres adhere to the ISHLT guidelines for CLAD detection, except of limited access to body plethysmography and expiratory CT scans, which may hinder accurate CLAD phenotyping.

In terms of tests used for CLAD monitoring, the results are congruent with those described at diagnosis, with both CT and DSA being preferred in the majority of patients. The ISHLT [4] recommends the use of

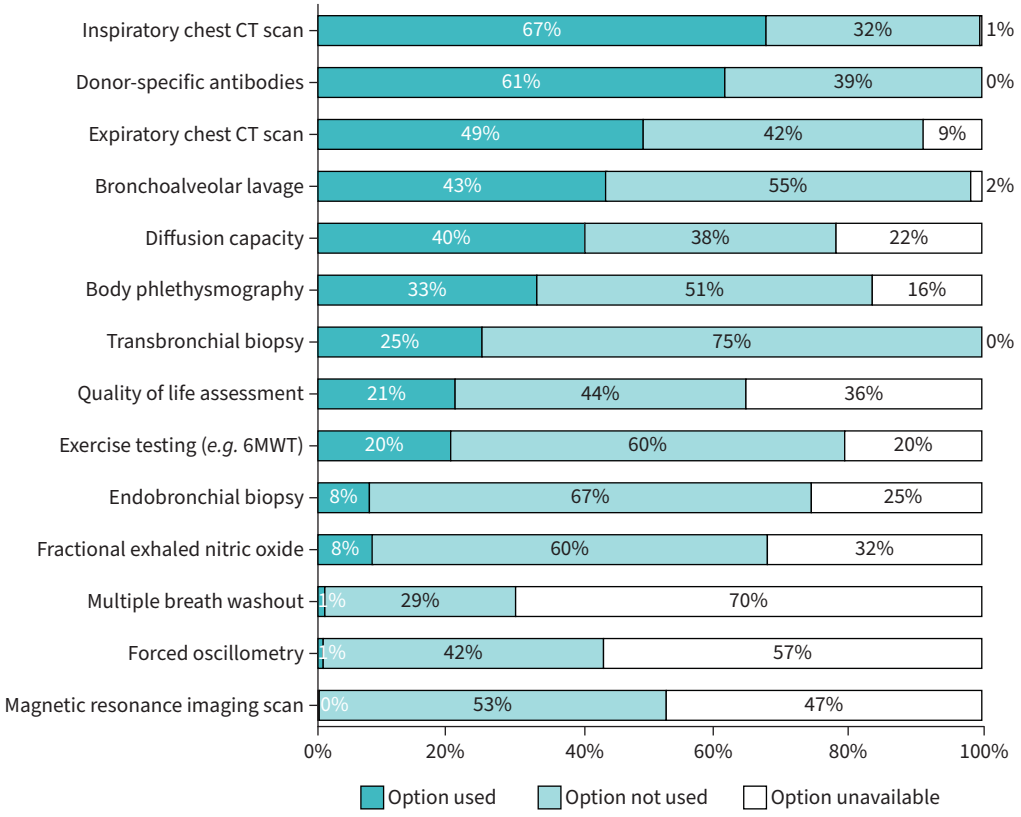

FIGURE 2 Technical monitoring of patients with definite chronic lung allograft dysfunction (CLAD) (n=44 centres). CT: computed tomography; 6MWT: 6-min walk test.

pulmonary function and imaging to assess treatment response in CLAD patients, even in stable CLAD patients, where spirometry is recommended every 3 or 4 months. The proportion of patients undergoing body plethysmography during follow-up was low in our cohort, considering the possibility of transition from BOS to RAS or mixed phenotype [12]. Although BAL and biopsies play a minor role in the follow-up of CLAD, this survey describes their use in a considerable proportion (43% of cases had BAL, 25% had TBB and 8% had biopsies). These follow-up bronchoscopies might be indicated for excluding other entities. Unfortunately, the sensitivity of TBB to diagnose bronchiolitis obliterans lesions is low, and therapeutic consequences regarding this are limited [13].

Regarding CLAD prophylaxis, some evidence from a small randomised trial supports the use of oral azithromycin, which was used in 72% of cases, in addition to conventional immunosuppression [14, 15].

There is a consensus to treat known clinical risk factors such as CMV infection (99% of cases) and chronic infections such as *Pseudomonas aeruginos*a (70% of cases are treated with inhaled antibiotics). Only 65% of patients receive antibiotic eradication treatment for chronic infection, although there is some evidence of benefit for graft survival [16]. In this study of 95 LTx recipients chronically infected with *P. aeruginosa*, eradication treatment was successful in 80% of cases and led to better lung function and longer graft- and CLAD-free survival. Inhaled antibiotics were not used in that study. It is also reasonable to optimise the treatment of chronic sinus disease with inhaled sinus antibiotics, utilised in fewer than 40% of our patients.

Although universal antifungal prophylaxis after LTx is commonly used, our data describe up to two-thirds of patients receiving prevention. This finding may be explained by a lack of evidence-based recommendations, local availability or reimbursement restrictions. The ISHLT consensus outlines two options (universal *versus* pre-emptive) with a class II level B recommendation but refrains from endorsing a specific protocol [17].

GERD is another risk factor associated with CLAD and is usually treated with universal PPIs. This is surprising as there is no evidence to support this practice, and PPIs may have adverse effects by increasing

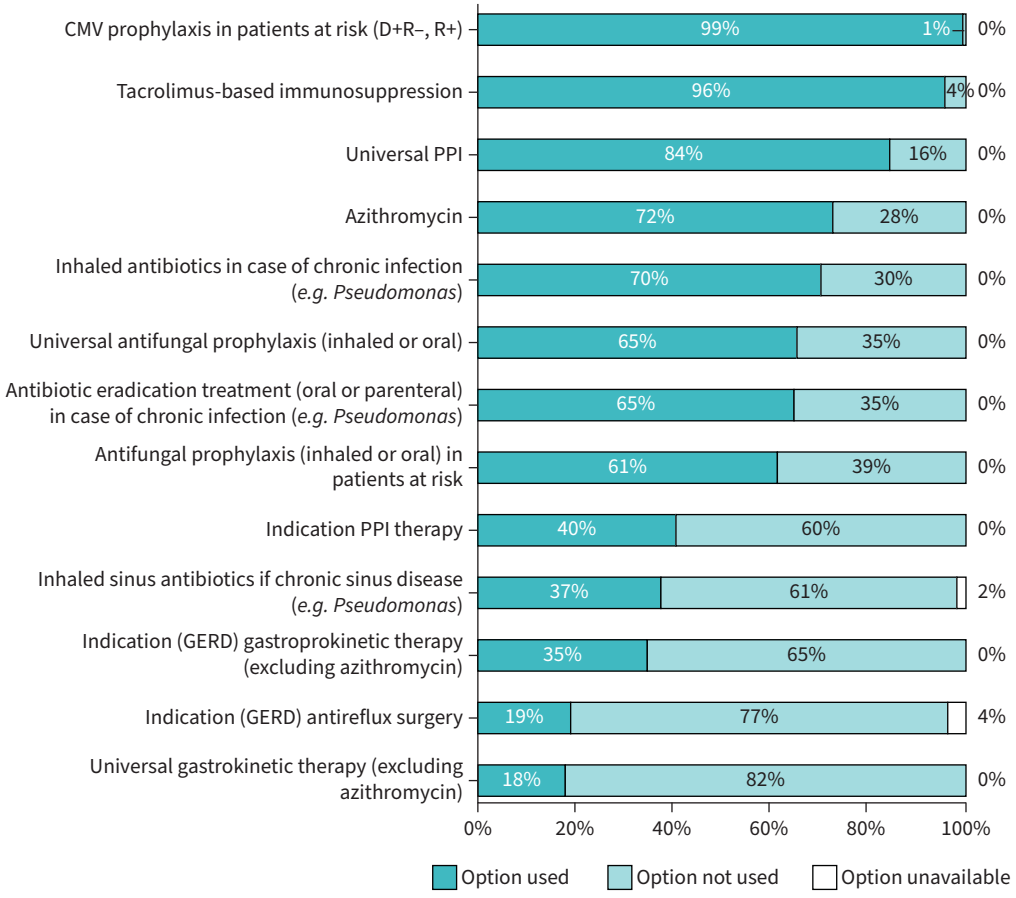

FIGURE 3 Options used for prophylaxis of chronic lung allograft dysfunction (CLAD) (n=44 centres). CMV: cytomegalovirus; D: donor; R: recipient; PPI: proton pump inhibitor; GERD: gastro-oesophageal reflux disease.

infection rates, promoting bone complications and causing leukopenia. In addition, PPIs do not affect non-acid reflux but this may be addressed by prokinetic therapy, including azithromycin. Surgical treatment for GERD is utilised in only 19% of cases. Limited evidence describing the benefits of surgery [18, 19], coupled with its availability only in specific centres, complicates the interpretation of data and the development of clinical trials. Nevertheless, the ISHLT/American Thoracic Society/European Respiratory Society guidelines [20] include referral to an experienced surgeon in therapy-refractory GERD for evaluation of fundoplication, although clinical results are controversial [21]. In summary, prophylactic treatment in Europe primarily relies on the evidence-based treatments azithromycin and tacrolimus-based immunosuppression [22] and addresses the most common risk factors. CLAD research should focus on prevention and treatment.

Finally, the survey provides insight into the lines of therapy for CLAD. Workup of potential CLAD patients is usually stepwise with noninvasive and simple tests used in the first line. No information was provided in which order tests were performed. The preferred first-line strategy is azithromycin and/or increasing steroids. Pulse steroids and azithromycin are not a treatment for CLAD *per se*, but rather to fully exclude acute rejection and azithromycin-responsive airway disease as an alternative diagnosis and is supported by ISHLT consensus. Long-term, high-dose corticosteroids are not recommended in the guidelines to avoid the harmful effects of ineffective therapies [20]. Bronchodilators are used in almost 40% of cases.

Extracorporeal photopheresis (ECP) and transitioning to mechanistic target of rapamycin inhibitors constitute the following lines of treatment, with heterogeneous use among centres. 10% of centres have no access to ECP. Both options are supported by a low level of evidence and randomised clinical trials are lacking. ECP is based on small, single-centre, retrospective studies showing long-term stabilisation in approximately 50% of patients [23, 24]. Similar outcomes have been reported for total lymphoid irradiation

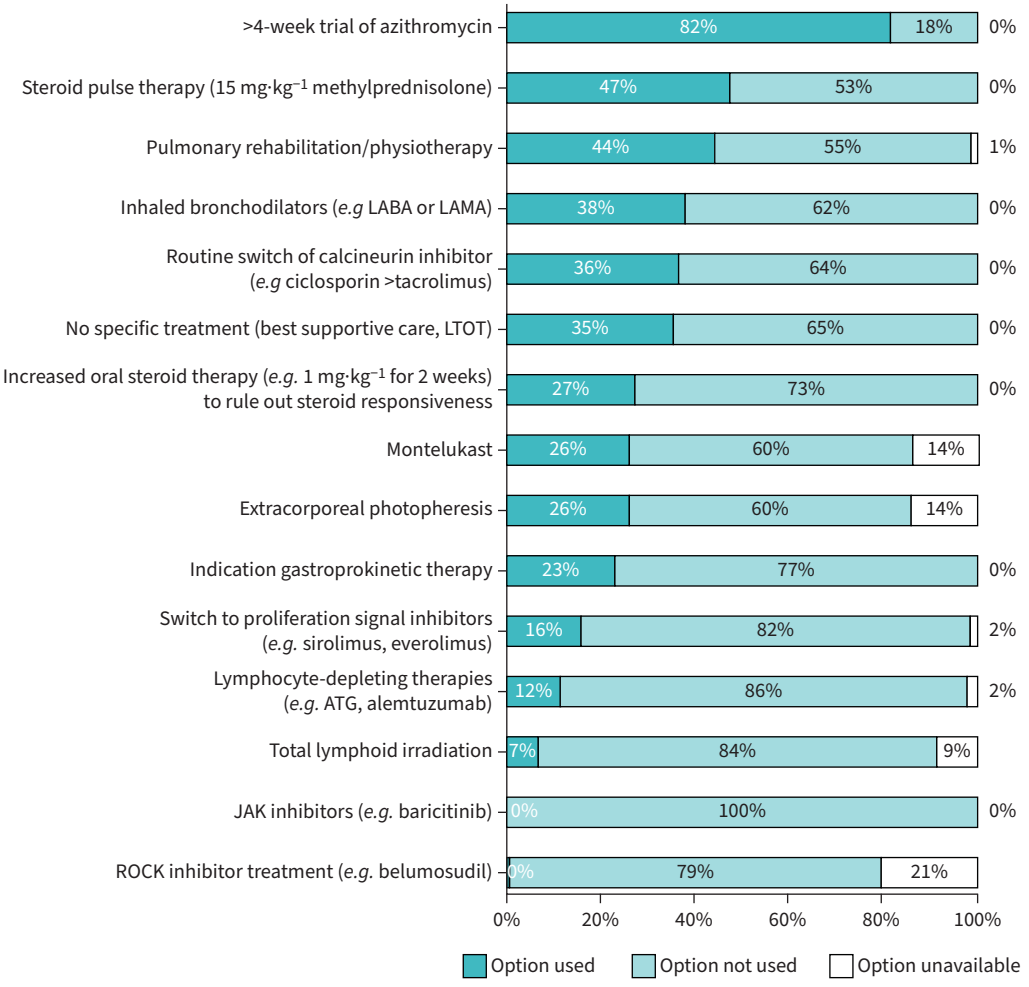

FIGURE 4 Options used for treatment of chronic lung allograft dysfunction (CLAD) (n=44 centres). LTOT: long-term oxygen therapy; LABA: long-acting β-agonists; LAMA: long-acting muscarinic agonist; ATG: anti-thymocyte globulin; JAK: Janus kinase; ROCK: Rho-associated protein kinase; mTOR: mechanistic target of rapamycin.

(TLI) [25, 26], also relying on single-centre retrospective studies. Although TLI has the advantage of being time-limited, it is used less frequently than ECP, which might be explained by higher toxicity Severe lymphopenia is described in up to 57% of patients [25], leading to early or temporary discontinuation in 20% of cases [26, 27]. 16% of centres report having no access to TLI. The use of montelukast in Europe is relatively infrequent (26%) and may be explained by negative results from a small randomised controlled clinical trial [3] contrary to BOS after allogeneic stem cell transplantation, in which the use of inhaled steroids (fluticasone), azithromycin and montelukast is recommended.

Anti-lymphocyte therapies such as anti-thymocyte globulin (ATG) or alemtuzumab are sporadically utilised, based on results from case series on their efficacy [28], alongside investigational drugs in clinical trials, mesenchymal stem cells or nintedanib. In summary, there is no single strategy universally applied across all centres, highlighting the limited level of evidence to support our practices and the desperate need for an effective treatment for CLAD. Moreover, the available studies restrict therapies to a selected subset of CLAD patients, complicating efforts to improve patient care.

Both ISHLT consensus documents [2, 20] suggest referral for re-transplantation evaluation, given the lack of effective therapies for CLAD. The need for careful selection of candidates and the limited availability of this complex option is reflected by its low use in our data.

As a limitation, respondents the survey relied on self-reported data: respondents may not have given accurate answers or collected data in the same way. The practices in nonresponding centres might skew the results.

TABLE 2 Chronic lung allograft dysfunction (CLAD) treatment preferences

First-line therapy		Second-line therapy		Third-line therapy and beyond	
	Of all centres (n=40)		Of all centres (n=40)		Of all centres (n=39)
azithromycin	19 (48)	photopheresis	7 (18)	photopheresis	19 (49)
steroid pulse intravenous	9 (23)	switch to mTOR inhibitor	6 (15)	consider re-do transplantation	8 (21)
steroids oral increase	4 (10)	steroid pulse intravenous	6 (15)	best supportive care	7 (18)
photopheresis	3 (8)	azithromycin	5 (13)	total lymphoid irradiation	6 (15)
switch calcineurin inhibitor	3 (8)	switch calcineurin inhibitor	4 (10)	montelukast	5 (13)
bronchodilators	3 (8)	reflux therapy	3 (8)	switch to mTOR inhibitor	4 (10)
montelukast	2 (5)	montelukast	3 (8)	steroids oral increase	4 (10)
steroids inhaled	2 (5)	anti-thymocyte globulin	3 (8)	steroid pulse intravenous	1 (3)
total lymphoid irradiation	1 (3)	bronchodilators	2 (5)	reflux therapy	3 (8)
increase immunosuppression	1 (3)	total lymphoid irradiation	1 (3)	anti-thymocyte globulin	3 (8)
rehabilitation	2 (5)	increase immunosuppression	1 (3)	alemtuzumab	3 (8)
best supportive care	1 (3)	rituximab	1 (3)	switch calcineurin inhibitor	2 (5)
		nintedanib	1 (3)	bronchodilators	2 (5)
		intravenous immunoglobulins	1 (3)	include in clinical trial	2 (5)
		include in clinical trial	1 (3)	increase immunosuppression	2 (5)
				mesenchymal stem cells	2 (5)
				azithromycin	1 (3)
				nintedanib	1 (3)
				rehabilitation	1 (3)
				steroids inhaled	1 (3)

Data are presented as n (%). mTOR: mechanistic target of rapamycin.

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Annual LTx activity in the European countries with missing data is 3–39 so we do not expect our results to be significantly different if they had responded to the questionnaire. Our results may not be fully generalisable depending on country-specific regulations or policies and local availability and reimbursement. Some promising experimental third-line treatments are expensive, and this limit the use of such therapies.

In summary, our survey indicates that CLAD is a rare disease, with a prevalence in Europe of around nine cases pmp. The current annual activity of LTx in Europe of 4.5 pmp highlights the burden of CLAD in LTx. LTx centres follow the ISHLT guidelines for CLAD detection, but some have limited access to body plethysmography and expiratory CT scans, which may hinder CLAD accurate phenotyping.

Prophylactic treatment in Europe is mainly based on evidence-based therapies: azithromycin, tacrolimus-based immunosuppression and management of the most common risk factors. There is no single treatment strategy that can be universally applied in all centres. The preferred first-line strategy is the optimisation of maintenance immunosuppressive treatment, azithromycin and/or increasing steroids. These results reflect the lack of specific treatment options in CLAD. Although there are positive randomised trials for CLAD prevention (tacrolimus and azithromycin) this has not led to licensing a specific drug to prevent the disease. There is an ongoing unmet need to prevent and treat rare diseases.

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References

1 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 Transplant* 2021; 40: 1060–1072.

2 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 Transplant* 2019; 38: 493–503.

3 Ruttens D, Verleden SE, Demeyer H, *et al.* Montelukast for bronchiolitis obliterans syndrome after lung transplantation: a randomized controlled trial. *PLoS ONE* 2018; 13: e0193564.
4 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: 442–450.
5 Le Pavec J, Valeyre D, Gazengel P, *et al.* Lung transplantation for sarcoidosis: outcome and prognostic factors. *Eur Respir J* 2021; 58: 2003358.
6 Verleden GM, Raghu G, Meyer KC, *et al.* A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant* 2014; 33: 127–133.
7 EDQM. Newsletter Transplant. *International Figures on Donation and Transplantation 2022*. Vol. 28. Strasbourg, EDQM, 2023.
8 Crowhurst TD, Butler JA, Bussell LA, *et al.* Impulse oscillometry versus spirometry to detect bronchiolitis obliterans syndrome in bilateral lung transplant recipients: a prospective diagnostic study. *Transplantation* 2024; 108: 1004–1014.
9 Fu A, Vasileva A, Hanafi N, *et al.* Characterization of chronic lung allograft dysfunction phenotypes using spectral and intrabreath oscillometry. *Front Physiol* 2022; 13: 980942.
10 Vogel-Claussen J, Kaireit TF, Voskrebenzev A, *et al.* Phase-resolved functional lung (PREFUL) MRI-derived ventilation and perfusion parameters predict future lung transplant loss. *Radiology* 2023; 307: e221958.
11 Wijbenga N, Hoek RAS, Mathot BJ, *et al.* Diagnostic performance of electronic nose technology in chronic lung allograft dysfunction. *J Heart Lung Transplant* 2023; 42: 236–245.
12 Fuchs E, Levy L, Huszti E, *et al.* Significance of phenotype change after chronic lung allograft dysfunction onset. *Transpl Int* 2021; 34: 2620–2632.
13 Glanville AR. The role of surveillance bronchoscopy post-lung transplantation. *Semin Respir Crit Care Med* 2013; 34: 414–420.
14 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: 164–172.
15 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: 254–261.
16 De Muynck B, Van Herck A, Sacreas A, *et al.* Successful *Pseudomonas aeruginosa* eradication improves outcomes after lung transplantation: a retrospective cohort analysis. *Eur Respir J* 2020; 56: 2001720.
17 Husain S, Sole A, Alexander BD, *et al.* The 2015 International Society for Heart and Lung Transplantation Guidelines for the management of fungal infections in mechanical circulatory support and cardiothoracic organ transplant recipients: Executive summary. *J Heart Lung Transplant* 2016; 35: 261–282.
18 Razia D, Mittal SK, Fournier S, *et al.* Antireflux surgery versus medical management of gastro-oesophageal reflux after lung transplantation. *Eur J Cardiothorac Surg* 2023; 63: ezad063.
19 Green CL, Gulack BC, Keshavjee S, *et al.* Reflux surgery in lung transplantation: a multicenter retrospective study. *Ann Thorac Surg* 2023; 115: 1024–1032.
20 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: 1479–1503.
21 Frankel A, Kellar T, Zahir F, *et al.* Laparoscopic fundoplication after lung transplantation does not appear to alter lung function trajectory. *J Heart Lung Transplant* 2023; 42: 603–609.
22 Dellgren G, Lund TK, Raivio P, *et al.* Effect of once-per-day tacrolimus versus twice-per-day ciclosporin on 3-year incidence of chronic lung allograft dysfunction after lung transplantation in Scandinavia (ScanCLAD): a multicentre randomised controlled trial. *Lancet Respir Med* 2024; 12: 34–44.
23 Benazzo A, Bagnera C, Ius F, *et al.* A European multi-center analysis of extracorporeal photopheresis as therapy for chronic lung allograft dysfunction. *Transpl Int* 2023; 36: 11551.
24 Barten MJ, Fisher AJ, Hertig A. The use of extracorporeal photopheresis in solid organ transplantation-current status and future directions. *Am J Transplant* 2024; 24: 1731–1741.
25 Geng-Cahuayme AAA, Sáez-Giménez B, Altabas-González M, *et al.* Efficacy and safety of total lymphoid irradiation in different chronic lung allograft dysfunction phenotypes. *Clin Transplant* 2023; 37: e14891.
26 Lebeer M, Kaes J, Lambrech M, *et al.* Total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation: a single-center experience and review of literature. *Transpl Int* 2020; 33: 216–228.
27 Fisher AJ, Rutherford RM, Bozzino J, *et al.* The safety and efficacy of total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation. *Am J Transplant* 2005; 5: 537–543.
28 Bos S, Pradère P, Beeckmans H, *et al.* Lymphocyte depleting and modulating therapies for chronic lung allograft dysfunction. *Pharmacol Rev* 2023; 75: 1200–1217.