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Review

# Chronic Lung Allograft Dysfunction, a Review in 2023

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**Abstract**

Chronic allograft dysfunction (CLAD) is one of the leading causes of death after lung transplantation [1]. CLAD is a progressive and irreversible decline in lung function after transplant, manifested as an obstructive, restrictive, or mixed ventilatory impairment without any identifiable etiology as infection or acute rejection. Multiple risk factors have been associated with this condition. Despite its significant effect on the mortality of transplanted patients, there is still a lack of powerfully effective therapies for patients with CLAD. Avoiding and correcting risk factors and close patient monitoring is critical in preventing disease progression. This article will discuss CLAD, the risk factors for developing the umbrella of syndromes under this term, and the current treatment alternatives and management available up to 2023.

**Keywords**

Lung; transplant; dysfunction; CLAD; rejection; treatment

## 1. Introduction

Infection, cancer, and chronic allograft dysfunction (CLAD) are the principal long-term causes of death after lung transplantation [1]. CLAD causes an indolent decrease in the function of the lung allograft, impacting the patient's quality of life and ultimately shortening survival. The condition progresses from a minimally symptomatic irreversible decline in the spirometry to exertional dyspnea and then to significant symptoms, even at rest. CLAD is progressive, but can also presents sub acutely, with a minimum of 3 weeks of allograft dysfunction to make diagnosis [2]. Data published by the International Society for Heart and Lung Transplant (ISHLT) registry reports a fifty percent incidence of CLAD in the first five years after transplant and almost three-quarters of patients after ten years [3]. Over 50% of patients were reported to die primarily due to CLAD in a single-center retrospective analysis that followed patients for more than ten years [4]. Overall survival of lung transplant recipients has improved in recent years, especially within the first year [5]. However, the multiple risk factors for the development of CLAD and limited treatment options for this condition are still significant roadblocks to patients' long-term survival. In this article, we will review new advances in the management of CLAD and how these have impacted the quality of life and life expectancy of lung transplant recipients.

## 2. Chronic Lung Allograft Dysfunction

### *2.1 Evolution of CLAD and the Grading System*

Prior to the term CLAD being coined, any loss of lung function post-transplant was attributed to BOS. This is a physiologic definition, much like CLAD is as well. The need to define BOS emanated from the recognition that when patients lost lung function post-transplant it was mostly due to bronchiolitis obliterans (BO). However, BO is a pathologic entity that requires a tissue diagnosis. Bronchoscopy is relatively insensitive and the best way to diagnose BO is through a surgical lung biopsy. In order to circumvent this, the physiologic entity of "bronchiolitis obliterans syndrome" was hence proposed and defined in 1992. It took almost 2 decades to recognize that not all forms of post-lung transplant loss of lung function are due to BO and that patients can develop radiographic abnormalities associated with a permanent loss of lung function. Hence, the all-encompassing "umbrella" term chronic lung allograft dysfunction (CLAD) was first coined in 2010. This was endorsed by a consensus statement in the International Society for Heart and Lung Transplantation published in 2014 and subsequently refined in 2019, differentiating the reversible causes of graft dysfunction from CLAD and emphasizing the restrictive phenotype within the CLAD definition [6].

### *2.2 Definition*

Chronic Lung Allograft Dysfunction is defined by a decline in lung function that persists for more than three weeks, starting three months post-transplant, with no other identified cause. Patients qualify as having CLAD after a decrease in post-transplant baseline FEV1 of at least 20% from the best post-transplant value [6].

### *2.3 CLAD Phenotypes*

The various CLAD phenotypes include Bronchiolitis Obliterans Syndrome (BOS), Restrictive Allograft Dysfunction (RAS), as well as undefined and mixed phenotypes. Each phenotype has a specific definition based on pulmonary function test (PFT) parameters and findings on chest imaging. The most common phenotype is BOS, which presents as an obstructive ventilatory defect on PFTs (FEV1/FVC <70%) secondary to obliterative fibrosis of the small airways. In recent years, a new phenotype of CLAD has been described as restrictive allograft syndrome (RAS). RAs can presents with persistent subpleural predominant fibrosis, bronchiectasis, reticular parenchymal changes and multi-lobar opacities, and a restrictive pattern on PFTs, which include a decrease in total lung capacity of >10% [6]. This phenotype includes chest image changes that most commonly demonstrate upper lobe fibrotic changes, but may include ground glass opacities and peripheral, basal fibrosis, with reticular changes that persist for at least 3 months [6]. There are also a mixed and an undefined phenotype that include both obstruction and/or restriction with or without persistent image changes. Some patients can present with an obstructive graft dysfunction that can be partially or completely reversible with azithromycin, and is called azithromycin-responsive allograft dysfunction, or ARAD [2]. These patients show a pro-inflammatory profile in the lung, with neutrophil count of more than 15% in the bronchoalveolar lavage without evidence of infection [7]. Unlike CLAD, that is primarily progressive and irreversible, patients with ARAD show improvement in lung function parameters after treatment with low dose azithromycin [7]. Is thought that around 40% of patients with suspected BOS respond to azithromycin with an increase in their FEV1 of at least 10% [2], and those patients usually presents with bronchial neutrophilia. However, neutrophilia in the bronchoalveolar lavage can also occurs in BOS, especially if the patient has over imposed infection.

### *2.4 Severity of CLAD*

The severity of CLAD is based on the decrease of FEV1 from baseline. Once the FEV1 decreases to ≤80% of the best baseline, serial categorical decreases of 15% define each stage of progression in CLAD (Figure 1) [6]. As expected, a decrease in lung function measured implies an increase in mortality, with a study suggesting a threefold increase in mortality with each 1% loss of FEV1 [8].


**Figure 1** CLAD severity staging.

For years, multiple therapies have been considered as a means to treat or at least slow the progression of the disease. These include identifying and mitigating risk factors as well as medical interventions intended to maintain lung function.

## 3. Risk Factors and Causes of CLAD

The pathologic events driving the development of CLAD have not been well categorized. For years CLAD was primarily thought to be a sequela of rejection, however, as new risk factors have been identified, the disease is felt to represent allograft tissue remodeling to multiple internal and external stimuli [8]. Recipient pre-existent conditions, as well as post-transplant immunologic and non-immunologic complications, have been highly associated with an increased risk of CLAD.

Pre-transplant HLA antibodies may predispose patients to antibody-mediated rejection and eventually to CLAD after transplant [9]. Koutsokera et al. [9] published a series of more than 400 pts, where the detection of donor-specific antibodies (DSA) was an early marker associated with the development of graft dysfunction. Some studies have suggested that the presence of pre-transplant HLA antibodies does not impact the risk of development of CLAD and mortality [10]. However, recent literature suggests that pre-transplant HLA antibodies are associated with worse waitlist and post-transplant survival, as well as higher rates of acute cellular rejection and BOS [11].

The treatment of patients with donor specific antibodies (DSA) without clinical or histopathologic evidence of rejection has also been shown to prolong the time to development of CLAD [11]. In addition, the severity and frequency of acute cellular rejection are directly correlated with the risk of developing CLAD [12]. While some publications propose that asymptomatic acute cellular rejection has not been associated with the development of CLAD [13], others suggest that multiple biopsies showing subclinical A1 rejection correlate with the eventual development of CLAD [12].

Gastroesophageal reflux (GER) is common following lung transplantation and is thought to predispose to the development of CLAD. Chronic aspiration is linked to increased pro-inflammatory cytokines, recruitment of alveolar inflammatory cells, and a reduction of surfactant proteins and anti-proteolytic mechanisms that protect the lung. [14] GER has also been associated with the development of acute cellular rejection, which is another mechanism whereby it might predispose to the development of CLAD [14]. Aggressive therapy for GER such as fundoplication has been shown to improve survival, even in patients with established CLAD [15].

Infection is a well-known cause and driver of progression of CLAD. Viral, bacterial, and fungal infections have all been implicated in the development of acute and chronic rejection and the loss of lung function. Viral infections have been associated with progressive loss of lung function, especially those that cause pneumonia, such as adenovirus and parainfluenza [16]. Detection of Cytomegalovirus (CMV) in the blood of transplanted patients is also associated with the development of BOS. However, high levels of CMV viral load in the BAL have not been associated with the development of CLAD, suggesting that the virus acts more as an activator of the immunologic system rather than acting as a direct trigger of the chronic rejection process [17]. Covid-19 infections after transplant are associated with high mortality in patients requiring hospitalization [18]. A multicenter retrospective study showed that transplanted patients may develop a restrictive ventilatory impairment that can last more than three months after Covid-19 infection; however, the effect on lung function in the long term remains to be determined [18]. Other viruses as Respiratory syncytial virus (RSV), parainfluenza virus (PIV) and human

metapneumovirus (hMPV) have been linked to an almost 20% risk of developing CLAD after a severe infection [19].

Bacterial infections have also been associated with CLAD, with the most commonly identified being *S. aureus* and *P. Aeruginosa. B*oth infection and colonization by these organisms have been shown to increase the risk of CLAD [20]. *Pseudomonas* is known to cause activation and proliferation of T cells and promote acute and chronic rejection [20]. Other microbes in transplanted patients, such as fungal infections, have also been identified as possible triggers for both acute lung allograft dysfunction and CLAD. In this regard, invasive *Aspergillus* infection as early as the first-month post-transplant has been identified as a risk factor for the development of CLAD [21]. Even colonization with this fungus has been linked to decreased lung function [22]. For this reason, most centers use three to six months of universal antifungal prophylaxis to reduce the risk of early colonization and invasive infection [20].

Other risk factors associated with the development of CLAD include the primary diagnosis leading to lung transplant and the development of primary graft dysfunction (PGD) in the immediate post-operative period [23, 24]. The lung damage caused by the inflammatory process during severe PGD prime the adaptive immune response against the allograft increasing the risk of rejection and CLAD [19]. Patients with a diagnosis of pulmonary fibrosis and cystic fibrosis have a higher incidence of CLAD than other lung transplant indications [23]. A body mass index (BMI) greater than 30 increases the risk of developing PGD, and consequently the risk of CLAD [25].

Lungs from smoking donors, high oxygen concentration (>40% FIO2), and tidal volumes >8 ml/kg during lung reperfusion are associated with greater severity of primary graft dysfunction and, as a consequence, increased risk of CLAD. Bilateral lung transplant recipients do not have a lower incidence of CLAD compared to a single lung transplant recipients, but they do have a reduced mortality after it presents [25].

### *3.1 Natural History and Progression of CLAD*

The development and progression of CLAD after transplant depends on the interaction of all identified post-transplant risk factors, the primary disease diagnosis of the recipient, and the donor's characteristics. It is well known that more than 50% of lung recipients will develop graft dysfunction at five years, with an average post-transplant survival of 6 years [26]. When CLAD is identified, the prognosis also depends on the phenotype, with the RAS phenotype having the worst survival rate [27]. In addition, the BOS grade is also associated with mortality; specifically each incremental increase in grade is associated with a three-fold increase in mortality [27]. Monitoring lung volumes in patients with BOS will identify patients with significant hyperinflation (RV/TLC >50%), which is also a sign of early mortality [28]. Early identification and treatment for acute rejection, controlling risk factors, using infectious prophylaxis, and interventions such as azithromycin have been strategies to prolong CLAD-free time and survival after transplant.

## 4. Strategies to Prevent CLAD

The first line of defense against CLAD is protecting the patient from the known risk factors. Patients should maintain a healthy body weight, as a BMI of >30 kg/m$^2$ as an independent risk factor for the development of CLAD [29]. Monitoring and treating for GER may also mitigate the risk of CLAD. Transplant candidates should have routine GER diagnostics performed during the pre-

transplant evaluation, which allows for early medical and surgical interventions. The institution of acid suppressant therapy in at risk patients before and after transplant is warranted and has been shown to decrease risk of both acute and chronic rejection. Delaying treatment for GER in the first six months after transplant has been shown to double the risk of CLAD [30]. At risk patients with scleroderma who underwent lung transplant and fundoplication thereafter have been shown to have prolonged CLAD free time and improved survival [31]. Given the available data, periodic monitoring for symptoms of GER and objective testing in patients with recurrent or recalcitrant rejection, could be a strategy to decrease the rate of CLAD progression in transplant recipients. The use of prokinetic agents, as metoclopramide, will promote bolus clearance and gastric emptying, decreasing episodes of reflux [15]. Surgery, and gastric peroral endoscopic myotomy are reasonable options for patients with evidence of GER and delayed gastric emptying despite acid suppressant therapy and prokinetics.

Early diagnosis of rejection allows one to identify modifiable risk factors to prevent further episodes as well as institute therapy expeditiously. Asymptomatic loss of lung function may be a harbinger of CLAD. Therefore, serial lung function testing has been the bedrock tool for the early identification of CLAD. Analysis of CT images can be used to rule out other causes of declining lung function and to identify early abnormalities secondary to CLAD. A high resolution chest CT should be obtained in all transplant recipients approximately six months after their lung transplant to establish a radiographic baseline, with a repeat study if ≥10% drop in lung function is identified [31]. Patients with early CLAD usually have more early abnormal findings and higher quantitative image scores for the extent of ground glass opacities, fibrosis, honey-combing and air trapping [32].

Transbronchial lung biopsies are typically performed to assess for evidence of acute cellular or antibody mediated rejection as routine surveillance or in patients with worsening lung function. Identifying CLAD with transbronchial biopsies has a low yield, but findings such as organizing pneumonia and bronchial eosinophilia can suggest CLAD in the appropriate clinical context [33].

Acute cellular and antibody mediated rejection are known risk factors for the development of CLAD. In addition, circulating donor specific antibodies have been linked to the developing of acute rejection and CLAD. Persistence of high levels of donor specific antibodies has been associated with the RAS phenotype in particular [33]. Plasma levels of donor-derived cell free DNA (dd-cfDNA) from the lung allograft increase during episodes of rejection, and thresholds with high sensitivity and negative predictive value have been established to detect rejection, even in asymptomatic patients [28]. Routine monitoring of these markers has been adopted by multiple transplant centers to facilitate the early diagnosis and treatment of acute and chronic rejection.

## 5. Therapy for CLAD

Specific therapy for CLAD has been of limited efficacy. Optimizing maintenance immunosuppression and treating acute events of rejection have been the cornerstones of CLAD treatment. Maintenance immunosuppressive therapy for lung transplant recipients usually consists of a calcineurin inhibitor such as cyclosporin or tacrolimus, an antimetabolite medication and systemic corticosteroids. A study of lung transplant recipients with BOS described a decrease in the rate of loss of lung function after changing from cyclosporine to tacrolimus [34]. The study demonstrated that patients on tacrolimus had fewer episodes of acute rejection, and less bacterial infections, both of which have been associated with the development of CLAD. Given this,

tacrolimus is the first line of immunosuppression used by most transplant centers, and is usually only substituted with cyclosporin or calcineurin free regimes when intolerable side effects or significant renal dysfunction occur. The antimetabolite drugs reduce lymphocyte cell proliferation by interfering with DNA synthesis. The most common antimetabolite medications used are mycophenolate mofetil (MMF) and azathioprine (AZA). A follow up study of patients with BOS demonstrated stabilization of lung function almost a year after starting MMF [35]. A retrospective study following patients with cyclosporine, steroids and either AZA or MMF identified less episodes of ACR and a smaller decline in lung function in those patients on MMF [36]. The use of MMF may also be associated with less need for systemic steroids [37]. Thus, a combination of MMF and tacrolimus are the principal post-transplant immunosuppression combination based on their association with a reduced incidence of CLAD. Azithromycin is a macrolide antibiotic shown to decrease neutrophilic inflammation and decrease levels of interleukin 8 [38], which is thought to be a mediator in the pathogenesis of CLAD. A meta-analysis published in 2017, showed that initiating azithromycin three weeks after transplant was associated with a lower incidence and severity of CLAD [39]. Also azithromycin improves esophageal motility and accelerates gastric emptying, reducing the risk of aspiration, itself a risk factor for CLAD [38].

Montelukast has been shown to improve pulmonary function in patients who develop obliterative bronchiolitis after graft versus host disease following bone marrow transplantation [40]. A pilot study published in 2011 showed a slower rate of decline in FEV1 with montelukast when compared to similar control cases [41]. There was no mortality benefit seen with the use of montelukast in a randomized control trial, but a post-hoc subanalysis suggested a delay in lung function decline in patients with Stage 1 BOS [42].

Lymphocyte depleting drugs have also been considered as part of the treatment algorithm of CLAD. Alemtuzumab is a recombinant monoclonal antibody directed against CD52, that can induce a prolonged lymphocyte depletion through cytolysis, and it use in early stages of BOS patients suggest that it can decrease lung function decline with a reduced efficacy in more advanced CLAD [19].

Extracorporeal photopheresis (ECP) removes activated lymphocytes through leukopheresis, then exposes the cells to a drug that later is activated by ultraviolet light decreasing the immune reaction. A ten-year lung transplant center experience described a slower rate of lung function decline in patients with BOS treated with ECP [36]. Follow up studies of patients treated with ECP for ACR have also shown improved survival [37], particularly in patients with the BOS phenotype without an increased risk of infections or significant adverse events [19]. Also ECP have shown improvement in lung function independently of CLAD stage and duration at treatment initiation [19]. In some publications this is considered as the first line of therapy for CLAD after optimizing immunosuppression.

The use of tumor necrosis factor alpha (TNF$\alpha$) inhibitors have been also considered in the treatment of CLAD. TNF cause inflammation and tissue damage by upregulation of various cytokines, and growth factors, and is thought to have some role on the development of rejection and CLAD. In a study with five patients with BOS, lung function and 6 minute walk distance improved in 4 patients, and all patients remained stable for at least 18 months [19].

Preliminary data in kidney transplant patients suggest that the use of interleukin 6 blockage and JAK inhibitors may be effective strategies to decrease rejection [43], but there is thus far no data in lung transplant patients.

Lung re-transplantation is a consideration in patients with end-stage CLAD. However, this is only an option for a minority of highly select patients and despite this survival outcomes are significantly lower compared to initial transplantation [44].

## 6. Conclusion

CLAD is one of the principal causes that limit the lifetime of the lung allograft. Reducing risks factors, early identification of episodes of rejection, and early initiation of available treatment options are the only tools available to decrease CLAD. New therapeutic options are currently on development including medications to control anti-inflammatory signaling, as JAK inhibitors, and cell control and regulation based therapies that target donor memory T cells after the allograft implantation [44]. Studies of novel agents to treat CLAD are sorely needed for this common and potentially devastating complication which remains the "Achilles heel" of lung transplantation.

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## Author Contributions

Onix J Cantres-Fonseca, Shambhu Aryal, Christopher King, and Steven D. Nathan contributed equally to this work. All authors make equal contributions to writing and editing the document.

## Competing Interests

The authors have declared that no competing interests exist.

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