



Detection, classification, and management of rejection after lung transplantation

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Abstract: Rejection is a major complication following lung transplantation. Acute cellular rejection, lymphocytic bronchiolitis, and antibody-mediated rejection (AMR) are all risk factors for the subsequent development of chronic lung allograft dysfunction (CLAD). Acute cellular rejection and lymphocytic bronchiolitis have well defined histopathologic diagnostic criteria and grading. Diagnosis of AMR requires a multidisciplinary approach. CLAD is the major barrier to long-term survival following lung transplantation. The most common phenotype of CLAD is bronchiolitis obliterans syndrome (BOS) which is defined by a persistent obstructive decline in lung function. Restrictive allograft dysfunction (RAS) is a second phenotype of CLAD and is associated with a worse prognosis. This article will review the diagnosis, staging, clinical presentation, and treatment of acute rejection, AMR, and CLAD following lung transplantation.

Keywords: Acute cellular rejection; antibody-mediated rejection (AMR); chronic lung allograft dysfunction (CLAD)

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Introduction

Despite advances in surgical techniques and recipient and donor selection, survival following lung transplantation remains worse compared with other solid organ transplantation with a median survival of 6 years (1). Graft failure is responsible for 22.7% of deaths between 30 days and 1 year following transplant. After the first year, chronic lung allograft dysfunction (CLAD) is the leading cause of death. Multiple factors likely contribute to high rates of rejection following lung transplantation, including increased susceptibility of the lung to injury and infection as well as constant environmental exposure (2). This article will review the clinical and pathologic features of and treatment options for acute cellular rejection (ACR), acute airway rejection, antibody-mediated rejection (AMR), and CLAD.

Acute rejection

The incidence of acute rejection varies depending on the lung transplant population and data source. The registry of the International Society of Heart and Lung Transplantation (ISHLT) reports 28% of lung transplant recipients experience at least one episode of treated acute rejection in the first year following transplantation (1). The Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients report from 2016 notes a lower incidence of acute rejection at 17.1% in the first year post transplant (3). Randomized controlled studies of different immunosuppressive regimens following lung transplantation describe higher rates of rejection. In a study of mycophenylate versus everolimus in combination with cyclosporine, rates of acute rejection were 46% and

Table 1 Pathologic grading of acute cellular rejection (8)

Grade	Severity	Description
A0	None	Normal parenchyma
A1	Minimal	Scattered, infrequent perivascular mononuclear infiltrates that are 2–3 cells thick
A2	Mild	More frequent perivascular mononuclear infiltrates that are readily recognizable at low magnification; infiltrates may include lymphocytes, macrophages, and eosinophils
A3	Moderate	Dense perivascular mononuclear infiltrates commonly associated with endothelialitis; extension of inflammatory cell infiltrate into alveolar septa and airspaces; eosinophils and occasional neutrophils are common
A4	Severe	Diffuse perivascular, interstitial, and air-space infiltrates of mononuclear cells; alveolar pneumocyte damage and endothelialitis

38% respectively in the first year after transplantation (4). In another study of tacrolimus and cyclosporine, 44% of all patients had at least one episode of A1 rejection and 49% had at least one episode of A2 rejection (5). Snell *et al.* found that everolimus significantly reduced the incidence of treated A1 rejection in the first year compared with azathioprine (7.9% *vs.* 32.1% respectively) (6). In a more recent study of the incidence of donor specific antibodies following lung transplantation, 64% of patients had at least 1 episode of acute rejection grade A1 or higher and 40% had one episode of rejection grade A2 or higher (7). The differences in the incidence of acute rejection in these studies are likely due to differences in protocols and timings of transbronchial biopsies, patient populations, and criteria for treatment.

The diagnosis of acute rejection is made based on the presence of perivascular and interstitial mononuclear cell infiltrates in lung tissue (8). The diagnosis is most often made based on transbronchial biopsies obtained bronchoscopically. At least five pieces of alveolated lung parenchyma are recommended for the assessment of acute rejection (8). The histologic grade of acute cellular rejection is dependent on the intensity of the perivascular mononuclear cell cuffs and the depth of mononuclear invasion into the interstitial and alveolar spaces with grades ranging from A0 (no rejection) to A4 (severe acute rejection) (8). *Table 1* summarizes the grading criteria for acute cellular rejection.

Lung transplant recipients with acute rejection may be asymptomatic or may present with non-specific symptoms such as dyspnea, cough, sputum production, and low-grade fever. Symptoms may be more frequent in patients with grade A2 or higher rejection compared with those with grade A0 or A1 (9). Although lymphocytic pleural

effusions may be associated with acute rejection (10), it is also reported in patients without acute rejection (11). Multiple studies have demonstrated that acute rejection is a risk factor for the development of bronchiolitis obliterans syndrome (BOS), the major form of CLAD. Increased severity of rejection and number of episodes of rejection increase the risk of BOS (12). Multiple episodes of A1 rejection as well as even a single episode are also associated with increased risk of BOS (13,14).

Because acute rejection is a risk factor for BOS, detection and treatment are important. However, the role of surveillance bronchoscopy for screening asymptomatic patients for acute rejection remains controversial, and performance of surveillance bronchoscopies varies depending on the transplant center. A 2004 survey of lung transplant centers in North America found that 69% of centers performed surveillance bronchoscopies (15). However, the data supporting surveillance bronchoscopies is mixed. In a single-center study in which some patients were monitored by surveillance bronchoscopy and others underwent clinically-indicated bronchoscopy, Valentine *et al.* found no differences in acute rejection, infection, or bronchiolitis obliterans-free survival between the two groups (16). More bronchoscopies were performed in the surveillance group compared with the clinically indicated group. In another prospective study of all bronchoscopic procedures at a single center, complication rates over 12 months were similar in patients who underwent surveillance bronchoscopies and those who underwent clinically indicated procedures, and approximately 18 percent of patients undergoing surveillance bronchoscopy were found to have acute rejection grade A2 or higher (17). Surveillance bronchoscopies may also detect other clinically relevant diagnoses such as infection (16,17). Centers who do not

Table 2 Pathologic grading of lymphocytic bronchiolitis (8)

Grade	Severity	Description
B0	None	No evidence of bronchiolar inflammation
B1R	Low grade	Mononuclear cells within the sub-mucosa of the bronchioles with occasional sub-mucosal eosinophils
B2R	High grade	Large and activated mononuclear cells, eosinophils, and plasmacytoid cells in the submucosa; evidence of epithelial damage with necrosis, metaplasia, and intra-epithelial lymphocytic infiltration
X	Ungradable	No bronchiolar tissue available

perform routine surveillance bronchoscopies may use lower thresholds to determine the need for clinically indicated bronchoscopies.

Lymphocytic bronchiolitis is characterized by airway inflammation without identifiable cause, such as co-existing infection. As shown in *Table 2*, lymphocytic bronchiolitis is graded as no airway inflammation (B0), low grade small airway inflammation (B1R), and high grade small airway inflammation (B2R) (8). Because there may be inadequate sampling of small airways in transbronchial biopsies, an ungradable category (BX) also exists for biopsies limited by sampling or processing problems. Lymphocytic bronchiolitis, independent of ACR, has been found to be a significant risk factor for both the development of BOS and death (18). Treatment of isolated lymphocytic bronchiolitis is controversial.

In general, there is consensus that acute cellular rejection grades A2 or higher require treatment. Treatment is generally with pulse corticosteroids, but there are no studies to define the optimal amount and duration of therapy. Most centers use intravenous methylprednisolone of 10–15 mg/kg daily or 500 to 1,000 mg daily for 3 days. An oral prednisone taper may follow. The management of asymptomatic minimal acute rejection (grade A1) remains controversial, despite its association with the development of BOS. Follow-up bronchoscopy may be performed to follow-up acute rejection in order to assess response to therapy or if untreated, rule out progression to a higher grade. Studies of the value of follow-up biopsies have shown that 26–44% of patients with moderate ACR have persistent rejection (19,20). There is no accepted, standardized regimen for treatment of persistent or refractory acute rejection. Reported approaches include additional intravenous glucocorticoids, antithymocyte globulin, alemtuzumab, total lymphoid radiation, and extracorporeal photopheresis (ECP) (21–23).

Antibody mediated rejection

AMR is a well-recognized entity following heart and kidney transplantation. Deposition of the complement split product C4d on the capillary endothelium has been suggested as a marker of AMR in other organ transplants. However, C4d immunofluorescence staining on lung tissue is a less reliable test, because of high background from non-specific binding, frequent focal staining, and presence of C4d deposition in infection and reperfusion injury (24). In addition, there is an unclear relationship between the presence of donor specific antibodies with graft damage and dysfunction, leading to difficulty in establishing a diagnosis in AMR. In 2016, a consensus document on AMR was published by ISHLT in order to standardize the diagnosis of AMR (25). This consensus statement divides AMR into two subtypes: clinical, defined by measurable allograft dysfunction, and subclinical, characterized by normal allograft function. AMR is then further sub-categorized into definite, probable, and possible based on the number of diagnostic criteria (25), with the greater number of criteria increasing diagnostic certainty. These criteria for definite AMR include: (I) exclusion of other causes such as infection; (II) histopathologic features; (III) presence of DSA; and (IV) positive C4d staining. Histopathologic features of AMR are non-specific and include neutrophilic capillaritis, neutrophil margination, acute lung injury with or without diffuse alveolar damage, and arteritis (26). A diagnosis of probable AMR lacks one criteria, a diagnosis of possible AMR lacks two criteria.

The true incidence and outcomes of AMR are unknown, since many reports of AMR were published before the current diagnostic criteria were established. In one center's series of 21 patients published prior to the most recent consensus statement, 21 cases of AMR were diagnosed in 501 lung transplant procedures (27). Of these 21 cases,

Table 3 Grading of bronchiolitis obliterans syndrome (31)

BOS grade	Spirometry % of baseline
0	FEV ₁ >90% and FEF _{25–75%} >75%
0-p	FEV ₁ 81–90% and FEF _{25–75%} ≤75%
1	FEV ₁ 66–80%
2	FEV ₁ 51–65%
3	FEV ₁ ≤50%

FEV₁, forced expiratory volume in 1 second; FEF_{25–75%}, forced expiratory flow 25–75%.

15 patients improved and were discharged from the hospital. Thirteen of the 14 discharged patients without pre-existing CLAD developed CLAD, and the median survival after diagnosis of AMR was 593 days. Patients who cleared DSA after therapy had better survival than those who did not. Another case series reported two patients with three markers of AMR out of 62 patients. Both of these patients had clinical improvement after treatment (28).

There is no standardized treatment for AMR, and there have been no randomized trials or head-to-head trials investigating AMR treatment. Common regimens for AMR treatment target the B-cell pathway and aim to deplete circulating antibodies and suppress B cells to prevent additional antibody formation. These regimens include intravenous immune globulin (IVIG), plasmapheresis, and rituximab alone or in combination. Additional agents such as carfilzomib or bortezomib, both of which are proteasome inhibitors, or eculizumab, an antibody targeting the C5 complement protein, may also be added (27,29).

CLAD

Chronic rejection is the major barrier to long-term survival following lung transplantation (1). CLAD includes both obliterative bronchiolitis (OB)/BOS and restrictive allograft dysfunction (RAS). OB is characterized by scarring or filling of the airway lumen seen on histopathology, leading to small airway obstruction. Because OB is difficult to diagnose by transbronchial biopsies or other non-invasive tests, BOS is clinically defined by pulmonary function measurements (30). It is defined by a decrease in the forced expiratory volume in 1 second (FEV₁) of at least 20% from the best baseline value, where the best baseline value is the average of the two highest post-transplant values obtained at least 3 weeks apart (31). Additionally, identifiable causes

such as acute rejection, infection, and anastomotic issues must be excluded. As seen in *Table 3*, BOS is graded based on the degree of decrease in FEV₁. Approximately 50% of lung transplant recipients develop BOS within 5 years after transplant (1). Median survival after a diagnosis of BOS is 3–5 years.

Although BOS is its most common form, CLAD is a heterogeneous condition with different phenotypes. RAS is being increasingly recognized as a second phenotype of CLAD. There are no universally accepted diagnostic criteria for RAS. In the first description of RAS, Sato *et al.* defined RAS as irreversible decline of FEV₁ to less than 80% of baseline in combination with an irreversible decline in total lung capacity (TLC) to less than 90% of baseline (32). RAS was further characterized by radiographic findings of upper lobe predominant fibrosis and histologically by diffuse alveolar damage and fibrosis in the alveolar interstitium, visceral pleural, and interlobular septa. Pleuroparenchymal fibroelastosis, with and without concomitant OB, was later identified as the major histopathologic finding in RAS (33). Verleden *et al.* (34) identified a group of patients with insufficient TLC data to diagnose RAS based on TLC, but found that these patients had a decrease in forced vital capacity (FVC) with a normal FEV₁/FVC ratio. The same group later proposed that a decrease in TLC ≥10% or a decrease in FVC ≥20% if no TLC was available could be used to diagnose RAS (35). Together, these studies determined that RAS accounts for approximately 25% to 35% of CLAD cases and has a worse prognosis compared with BOS with a median survival of only 6–18 months after diagnosis (32,35,36). The BOS and RAS phenotypes of CLAD are not mutually exclusive, and patients may evolve from one phenotype to the other.

Multiple factors have been identified as risk factors for the development of BOS. As discussed above, acute cellular rejection and lymphocytic bronchiolitis are risk factors for BOS and have also been identified as risk factors for the development of RAS (37). Other risk factors associated with BOS include primary graft dysfunction (38,39), presence of *de novo* donor specific antibodies (40,41), and presence of gastroesophageal reflux disease (42). Bacterial, fungal, and viral infections and colonization are also associated with BOS, particularly with *Pseudomonas aeruginosa* (43,44), *Aspergillus* (45,46), and cytomegalovirus (47).

Azithromycin, an immunomodulatory macrolide antibiotic, has been studied in the prevention and treatment of CLAD. Thirty to 83% of patients with BOS have

improvement in FEV₁ when treated with azithromycin (48). A proportion of patients continue to have decline in FEV₁ despite treatment (49,50). Responders tend to receive azithromycin earlier after transplantation (50). Some studies also suggest that responders have bronchoalveolar lavage neutrophilia (50,51), though other studies do not support this finding (49). In a small, randomized, controlled trial, prophylactic azithromycin led to decreased incidence of BOS and longer BOS-free survival (52). Azithromycin has also been shown to improve mortality in lung transplant recipients with BOS stage 1, but not stage 2 (53). In a post-hoc analysis with long-term follow-up of patients receiving azithromycin and placebo, use of azithromycin delayed the development of CLAD compared with placebo (54).

Montelukast, a cysteinyl leukotriene, has recently been studied as a potential treatment for CLAD. In a retrospective, single center study, treatment of lung transplant recipients with established CLAD with montelukast 10 mg daily attenuated the rate of decline of FEV₁ (55). Sixty-one percent of patients were free from CLAD progression, defined by a less than 10% decrease or increase in FEV₁. However, a small, randomized controlled study by the same group failed to demonstrate a survival benefit or difference in rate of change of FEV₁ with montelukast compared with placebo (56). Findings in this study were likely limited by a sample size of only 30 patients.

ECP, a procedure which removes lymphocytes from peripheral blood, exposes them to a photosensitizing agent followed by UV light, then returns the treated blood to the patient, has also been used in the treatment of BOS. ECP has been shown to reduce the rate of decline of lung function and improve survival in patients with BOS (57). A randomized study of ECP in Medicare recipients with BOS is currently enrolling (NCT02181257, www.clinicaltrials.gov). Other therapies for BOS include antithymocyte globulin, total lymphoid irradiation, and alemtuzumab, an anti-CD52 antibody (58). Finally, retransplantation is an option for patients with progressive CLAD despite treatment. Retransplantation has worse survival compared with initial transplant and a higher incidence of BOS in the first 5 years following transplant (1). Furthermore, patients with RAS phenotype have worse survival after retransplantation when compared with patients with BOS (59). Therefore, careful patient selection is important when considering retransplantation for CLAD.

Conclusions

Rejection remains a significant problem following lung transplantation. Acute cellular rejection, lymphocytic bronchiolitis, and AMR are all risk factors for the subsequent development of CLAD, the leading cause of death following the first year after transplantation. More information is needed to better identify and further refine phenotypes of CLAD, especially since treatment efficacy and prognosis differ for RAS compared with BOS. Randomized controlled trials are also needed to differentiate the effect of therapy from the natural course of the disease.

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Footnote

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