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# The role of the immune system in lung transplantation: towards improved long-term results

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**Abstract:** Over the past 35 years, lung transplantation has evolved from an experimental treatment to the treatment of choice for patients with end-stage lung disease. Beyond the immediate period after lung transplantation, rejection and infection are the leading causes of death. The risk of rejection after lung transplantation is generally higher than after other solid organ transplants, and this necessitates more intensive immunosuppression. However, this more intensive treatment does not reduce the risk of rejection sufficiently, and rejection is one of the most common complications after transplantation. There are multiple forms of rejection including acute cellular rejection, antibody-mediated rejection, and chronic lung allograft dysfunction. These have posed a vexing problem for clinicians, patients, and the field of lung transplantation. Confounding matters is the inherent effect of more intensive immunosuppression on the risk of infections. Indeed, infections pose a direct problem resulting in morbidity and mortality and increase the risk of chronic lung allograft dysfunction in the ensuing weeks and months. There are complex interactions between microbes and the immune response that are the subject of ongoing studies. This review focuses on the role of the immune system in lung transplantation and highlights different forms of rejection and the impact of infections on outcomes.

**Keywords:** Lung transplantation; rejection; infection; chronic lung allograft dysfunction (CLAD)

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## History of lung transplantation and introduction

Lung transplantation is a relatively young field. The first human lung transplant was performed in 1963 at the University of Mississippi (1). The recipient had emphysema and lung cancer obstructing the left mainstem bronchus and nephrotic syndrome. He underwent a left single lung transplant and was treated with mediastinal radiation, azathioprine, and steroids for immunosuppression. Post-operatively, he was weaned from ventilatory support, but died 18 days later due to complications of renal failure. Post-mortem examination of the lung showed no evidence of rejection. In spite of the poor outcome, this case illustrated that a single transplanted lung would function, and that rejection could be averted at least for a brief time with the available immunosuppression at the time (1).

Over the ensuing decade, 36 additional lung transplants were reported worldwide, but outcomes were uniformly poor (2). Many patients were moribund at the time of transplantation and would not be considered candidates today. Pneumonia, rejection, and respiratory failure were common causes of death, and there were no long-term survivors. Growing experience in heart and heart-lung transplantation paved the way for refinements in surgical techniques of lung transplantation. Additionally, the advent of cyclosporine and encouraging experience with its use in kidney transplantation facilitated the rebirth of lung transplantation (3,4). In 1983, the Toronto Lung Transplant Group performed the first successful lung transplant, and the results were reported as part of a two-patient series in 1986 (5). This was the beginning of lung transplantation in the modern era, and volumes rapidly increased as lung

transplantation emerged as the ultimate treatment for end-stage lung disease. In the latest International Society for Heart and Lung Transplantation (ISHLT) Registry report, over 4,600 lung transplants were performed in adults and children in 2016 (6). The indications span the spectrum of lung disease; interstitial lung disease (ILD), chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF) comprise approximately 80% of underlying diagnoses leading to transplant (6). Over the past 15 years, the volume of bilateral transplants has increased, and in 2016, 80% of all lung transplants reported to the ISHLT Registry were bilateral (6). Indeed, bilateral transplantation is associated with better long-term survival (6).

Lung transplantation improves survival and quality of life when timed appropriately (7-11). Furthermore, there has been a significant improvement in survival after lung transplantation over time, and the median survival in the most recent era between 2009 and 2016 is 6.5 years (6). However, survival after lung transplantation remains significantly worse than after kidney, heart, and liver transplantation (12-14). Early after lung transplantation, infection and allograft failure due to primary graft dysfunction (PGD) are the leading causes of death; however, chronic rejection, termed chronic lung allograft dysfunction (CLAD), is the primary cause of death beyond the first year after transplantation, accounting for approximately 40–50% of deaths (6). Infection remains a significant problem at all time points, and according to the ISHLT Registry, 15–20% of deaths beyond the first year are due to infection (6). Thus, chronic rejection and infection account for up to 70% of deaths beyond the first year after lung transplantation. This underscores the critical role of the immune system and the delicate balance of appropriate immunosuppression after lung transplantation. More intensive immunosuppression may increase the risk and severity of infection and malignancy while less intensive immunosuppression increases the risk of rejection. Indeed, the inability to accurately gauge the degree of immunosuppression has been a significant challenge in clinical practice as the current approach of targeting various calcineurin inhibitor (CNI) trough levels or steroid or cell-cycle inhibitor dose is grossly imprecise.

## Rejection after lung transplantation

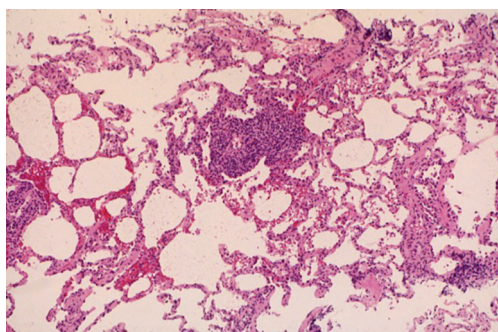
### *Hyperacute rejection*

Different forms of lung rejection exist, and an overview of

these is presented here. Hyperacute rejection is a fulminant form of lung rejection that occurs within minutes or hours of reperfusion of the allograft (15-18). In clinical practice, distinguishing hyperacute rejection from severe PGD can be difficult, and the results of histocompatibility testing are critical to establishing the diagnosis. Pre-formed donor-specific antibodies (DSA) cause hyperacute rejection. DSA are most commonly directed at mismatched human leukocyte antigens (HLA) although non-HLA antibodies may also cause hyperacute rejection (19). The paradigm for the pathogenesis of hyperacute rejection is that DSA bind HLA molecules on endothelial cells and activate the complement cascade which results in endothelial cell necrosis, exposure of the basement membrane, activation of the coagulation cascade and hemorrhagic infarction. Over the past 10 years, hyperacute rejection has become rare because of advances in HLA antibody detection methods. Indeed, solid phase assays have significantly improved the sensitivity and specificity of HLA antibody detection before transplantation (20,21). This allows transplant centers to identify unacceptable antigens for a sensitized patient on the waiting list and minimizes the possibility of a positive crossmatch and hyperacute rejection by avoiding the reactive HLA in a potential donor. Nevertheless, although hyperacute rejection has become quite rare, it demonstrates that antibodies can cause fulminant allograft rejection and that the capillary endothelium is the focal point of injury.

### *Acute cellular rejection (ACR)*

In contrast, ACR is a common complication after lung transplantation. In the ISHLT Registry, approximately 30% of adult lung transplant recipients experience at least 1 episode of ACR in the first year after transplantation (6). However, large international registries may underestimate the incidence of ACR because of reporting limitations. In fact, some randomized controlled trials comparing the efficacy of different immunosuppressive agents have reported an incidence of ACR that ranges between 40–50% (22,23). The highest incidence of ACR is in the first 6 months after transplantation. Non-invasive approaches to the diagnosis of ACR including imaging studies and pulmonary function tests are insensitive and typically non-specific. Consequently, transbronchial lung biopsy remains the gold standard for the diagnosis of ACR although the procedure is invasive and carries some risk of complications. According to the standard ISHLT definition of ACR, the characteristic histologic finding is the presence of a



**Figure 1** This transbronchial lung biopsy illustrates a case of mild acute cellular rejection (grade A2). A mononuclear cell infiltrate that expands the vascular adventitia is easily visible at low magnification. Hematoxylin and eosin staining,  $\times 40$ .

mononuclear cell infiltrate circumferentially surrounding small vessels (24–26). The severity of ACR is based on the intensity of infiltration and extension into the adjacent interstitium. Minimal ACR (grade A1) is characterized by scattered perivascular infiltrates that are not easily visible at low magnification. The perivascular infiltrates are identifiable at low magnification in mild ACR (grade A2), and the infiltrate comprises activated lymphocytes, macrophages, and eosinophils that expand the vascular adventitia (*Figure 1*). Extension of the mononuclear cell infiltrate into the adjacent interstitium and frequent, obvious infiltrates at low magnification are characteristics of moderate ACR (grade A3). Severe ACR (grade A4) is very rare, and is characterized by diffuse infiltrates with necrotizing vasculitis and diffuse alveolar damage.

Lower grades of ACR (e.g., A1 and A2) are typically clinically silent, and some cases of moderate ACR (grade A3) are asymptomatic. As a result, many transplant centers employ a surveillance bronchoscopy and transbronchial lung biopsy protocol to identify cases of ACR (27,28). There is no consensus on the utility of surveillance biopsies, and many centers advocate biopsies only if patients develop signs or symptoms of allograft dysfunction (29). Proponents of a surveillance protocol argue that early treatment of ACR may decrease the likelihood of higher grades of ACR or the development of CLAD although empirical evidence to support this is lacking. Nevertheless, historical data suggest that programs that do not use a surveillance protocol may perform an equivalent number of procedures because the threshold to pursue a clinically indicated biopsy may be lower (30).

There is little data about the natural history of ACR. In an early study, asymptomatic patients with mild ACR (grade

A2) who were not treated were followed clinically (31). Ten of 16 patients worsened: 4 had persistent A2 rejection, 4 progressed to A3 rejection, 1 developed obliterative bronchiolitis (OB), and 1 developed severe lymphocytic bronchiolitis (31). In addition, 5 of these 10 developed bronchiolitis obliterans syndrome (BOS) during the study follow-up (31). As a result, most patients with mild ACR (grade A2) are treated with bolus methylprednisolone. Furthermore, multiple studies have identified a significant association between ACR and the subsequent development of BOS (32–35). Indeed, even episodes of minimal ACR (grade A1) are associated with an increased risk of BOS (33–35). Nevertheless, although these studies have identified an association between ACR and BOS, this should not suggest that ACR causes BOS. Indeed, it is unclear how the perivascular inflammation characteristic of ACR would result in small airway fibrosis. It is possible that ACR is a marker of the underlying alloimmune response that causes BOS.

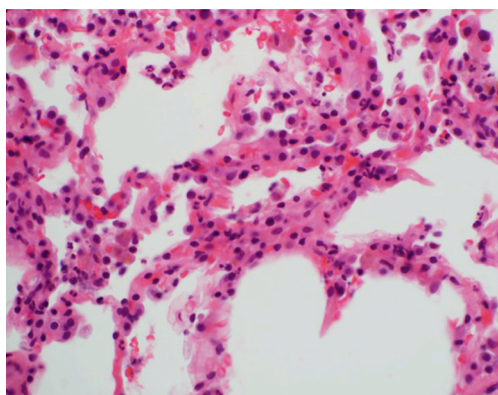
### *Lymphocytic bronchiolitis*

Lymphocytic bronchiolitis is characterized by peribronchiolar mononuclear cell infiltrates (26). This airway inflammation often accompanies higher grades of ACR and is considered airway directed acute rejection if there are no signs of a superimposed infection. The ISHLT working formulation for lung allograft rejection defines lymphocytic bronchiolitis grade B1R as submucosal peribronchiolar mononuclear cell infiltrates without epithelial damage or intra-epithelial lymphocytic infiltration (26). Grade B2R is defined as more intense inflammation with activated mononuclear cells including eosinophils and there is intra-epithelial infiltration and epithelial ulceration or necrosis (26). Previous studies have noted that lymphocytic bronchiolitis can be refractory to steroid therapy and is associated with an increased risk of BOS development and death (36,37). The evolution of epithelial ulceration and necrosis to fibrosis and luminal obliteration characteristic of OB is a reasonable explanation for this association. With this in mind, undiagnosed concomitant lymphocytic bronchiolitis may be the explanation for the association between ACR and BOS.

### *Antibody-mediated rejection (AMR)*

AMR is an increasingly recognized form of lung allograft rejection. In recent years, multiple case reports and case series from different centers describing the presentation and





**Figure 2** Neutrophilic capillaritis with neutrophils and karyorrhectic debris in the alveolar septa. Hematoxylin and eosin staining,  $\times 400$ .

clinical features of AMR have been published (38-45). Based on these findings and experience in kidney transplantation, the ISHLT developed a consensus definition for pulmonary AMR (46). According to this definition, the diagnosis of definite AMR is made if all of the following criteria are present:

- ❖ Clinical allograft dysfunction;
- ❖ Lung injury pathology;
- ❖ Capillary C4d deposition;
- ❖ Circulating DSA;
- ❖ Clinical exclusion of other possible causes of allograft dysfunction.

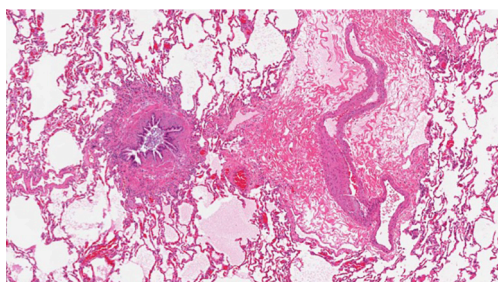
The diagnostic certainty is dependent on the number of criteria present. If one of the above criteria is absent, the diagnosis of AMR is considered probable, and if 2 of the above criteria are absent, the diagnosis is considered possible (46). However, because C4d staining and interpretation have been problematic in lung transplantation, the committee noted that a diagnosis of AMR can be confidently made in the absence of C4d deposition if all other criteria are present.

This ISHLT definition for pulmonary AMR will facilitate future research and standardize the diagnosis across centers. However, the definition is complex and relies on a multi-disciplinary approach. Indeed, the diagnosis of AMR remains a difficult one and requires a high index of suspicion. It is important to note that the histologic features are typically non-specific. These may include acute and organizing lung injury, pneumonitis, diffuse alveolar damage, capillaritis, and ACR. In the right clinical setting, neutrophilic capillaritis raises the suspicion for AMR (47,48). The characteristic findings are neutrophilic infiltration with karyorrhectic debris in alveolar septa (*Figure 2*). However,

neutrophilic capillaritis is not a sensitive finding. Although C4d deposition provides direct immunopathologic evidence of the effect of antibodies, many cases that have all other criteria are C4d-negative (43,45,48). Indeed, a recent relatively large single center study compared the clinical presentation, DSA characteristics, histologic findings, and outcomes of C4d-positive cases to C4d-negative cases of AMR (48). There were no significant differences between the two groups with the exception that C4d-negative cases were more likely to be due to non-complement binding DSA (48). The authors proposed that C4d-negative cases of AMR be considered definite AMR if all other criteria are present. In addition, they suggested that some C4d-negative cases might be due to complement-independent pathways (48). Furthermore, C4d-negative AMR is now a widely recognized form of AMR in kidney transplantation (49,50). The diagnosis of AMR remains difficult because of the absence of specific histologic findings and the inconsistencies of C4d staining. Confounding matters further, DSA are common but do not necessarily lead to AMR, and there are various causes of allograft dysfunction. Clearly, better diagnostics are necessary to facilitate the identification of AMR. Finally, although AMR may be a reversible form of allograft failure, there is a high incidence of CLAD among survivors (42-45,48).

### *Chronic lung allograft dysfunction*

As noted above, CLAD is the leading cause of death beyond the first year after lung transplantation (6). CLAD is stratified into two phenotypes with potential overlap between these. BOS is the prototypic form of CLAD and was recognized in the late 1980s as the critical barrier to better long-term outcomes after heart-lung and lung transplantation (51-54). OB, a fibroproliferative scarring of membranous and respiratory bronchioles that results in luminal obliteration, is the characteristic histology of BOS (*Figure 3*). However, the sensitivity of transbronchial lung biopsy for the diagnosis of OB is poor because of the small sample size and the patchy nature of OB. As a result, BOS is the clinical surrogate for OB and is defined based on obstructive changes in spirometry with progressive stages defined according to the magnitude of decrease from baseline (53,54). Restrictive allograft syndrome (RAS) has been recognized over the past 10-15 years as a more rapidly progressive form of CLAD (55-58). There are significant differences in spirometry and imaging studies between RAS and BOS. BOS is characterized by an obstructive



**Figure 3** Obliterative bronchiolitis with mural fibrosis and smooth muscle hypertrophy. Hematoxylin and eosin staining,  $\times 40$ .

ventilatory defect whereas RAS manifests with a restrictive ventilatory abnormality. A challenge to the diagnosis of RAS is that measuring total lung capacity (TLC) has not been a part of routine pulmonary function testing at most transplant centers. Thus, baseline values are not available for comparison at disease onset. The pathology of RAS has not been extensively studied. In one series of 16 patients with RAS who had available pathology specimens, 15 had pleuroparenchymal fibroelastosis and 1 had diffuse alveolar damage (59). It is noteworthy that 14 of the 16 patients had concomitant OB (59). This raises questions about whether RAS is truly a distinct and unique phenotype of CLAD or whether it represents a more advanced or severe form. Furthermore, in the original descriptions of OB as chronic lung allograft rejection after heart-lung transplantation, diffuse interstitial and pleural fibrosis as well as a concomitant restrictive ventilatory abnormality were noted (60,61).

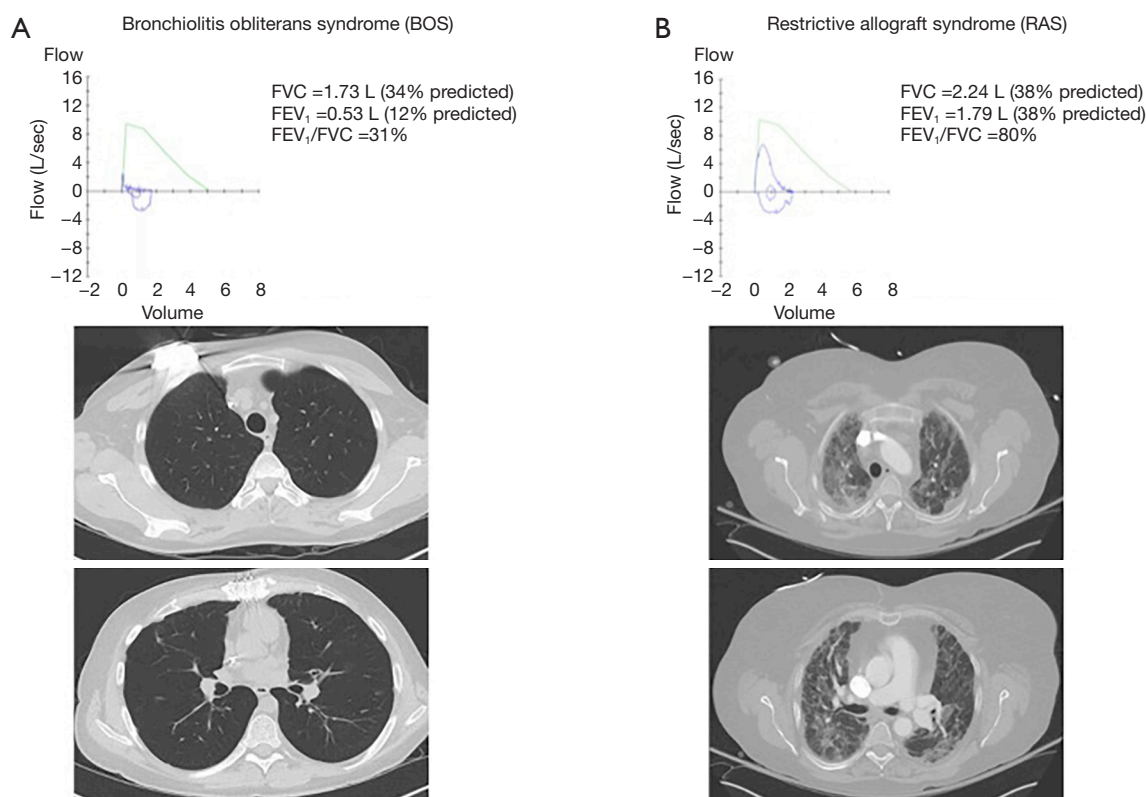
Patients with BOS typically have no abnormalities on chest X-ray or chest computed tomography (CT) until advanced stages where mosaic attenuation, bronchial dilation, or air trapping may appear (62). In contrast, upper lobe predominant coarse radiographic opacities on chest X-ray and CT scan are characteristic of RAS (55,57,58). *Figure 4* illustrates differences in spirometry and CT scan findings between a patient with advanced BOS (*Figure 4A*) and a patient with advanced RAS (*Figure 4B*). A clinical presentation with features of both BOS and RAS is possible. In addition, some patients may present with BOS at the onset of CLAD diagnosis and evolve into RAS and vice versa (57). *Figure 5* illustrates an example of a patient who progressed from BOS to RAS over time. The patient developed BOS 18 months after bilateral lung transplantation (*Figure 5A*). In spite of intensive treatment, CLAD progressed and by 54 months after transplantation, he had advanced RAS (*Figure 5B*). At autopsy, the patient

was noted to have extensive OB, interstitial fibrosis, and mild ACR.

Evidence-based treatment options for CLAD are limited. There has been only one randomized controlled trial for the management of CLAD where 48 patients with BOS were randomized to azithromycin or placebo (63). In this study, five patients who were randomized to placebo crossed over to open label azithromycin, and there was no significant difference between the azithromycin and the placebo group in the intention to treat analysis (63). However, among those who completed the study, azithromycin was associated with improved lung function compared to placebo (63). Beyond azithromycin, treatment options include bolus methylprednisolone, anti-thymocyte globulin, alemtuzumab, and extracorporeal photopheresis (64-69). In spite of aggressive treatment, the clinical course is typically progressive resulting in respiratory failure and death or re-transplantation in the majority of patients. The median survival after the diagnosis of BOS is approximately 2.5 years (70). However, survival after the diagnosis of RAS is significantly worse (57). Clearly, improved prevention and treatment of CLAD are necessary to improve patient outcomes after lung transplantation.

## Infection

Lung transplant recipients are at increased risk of infection at all time points, and infection is a common cause of death accounting for up to 20% of all deaths beyond the first year after transplantation (6). Therapeutic immunosuppression is necessary to mitigate the risk of rejection, but this inherently increases the risk of infection. Furthermore, local host defenses are impaired with the loss of lymphatic drainage and impaired mucociliary clearance and cough mechanism after lung transplantation. Lastly, the lung allograft is in constant contact with the environment, and this increases the risk of acquiring infections. In the immediate period after transplantation, donor-transmitted, recipient-derived, and nosocomial infections are most common. Typical donor-transmitted infections are bacterial pneumonia and community-acquired respiratory viral (CARV) infections. Mycobacterial and endemic fungal infections are less common, and systemic viral infections (e.g., human immunodeficiency virus, hepatitis C virus) are exceedingly rare with current donor testing protocols. Common nosocomial infections include bacterial pneumonia, surgical site infection, empyema, and *Clostridium difficile* colitis. In general, patients are treated with empiric broad-



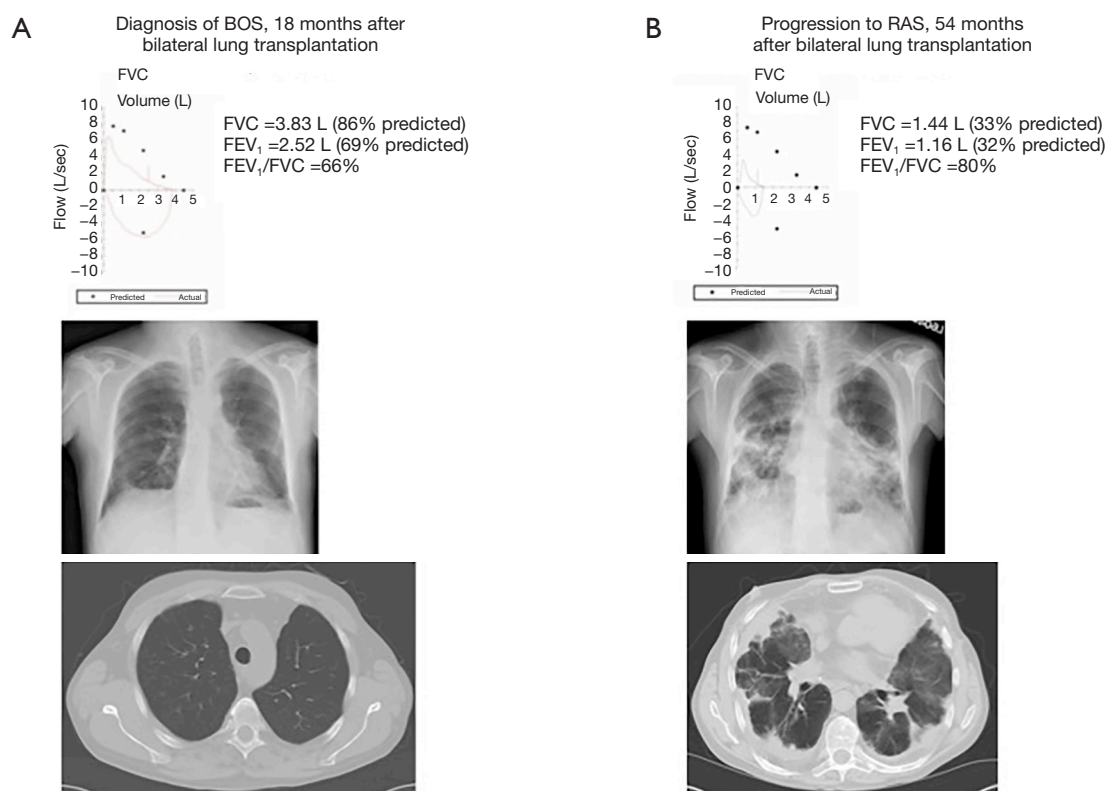
**Figure 4** Spirometry and chest computed tomography (CT) scan. (A) Spirometry and chest CT scan from a patient with advanced bronchiolitis obliterans syndrome (BOS) are illustrated. There is a severe obstructive ventilatory defect and a clear chest CT. (B) Spirometry and CT scan from a patient with advanced restrictive allograft syndrome (RAS) are illustrated. Spirometry shows reduction in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>) in a pattern suggestive of a restrictive ventilatory abnormality. CT scan illustrates coarse fibrotic interstitial opacities.

spectrum antibacterial antibiotics for the first 7–14 days after transplantation, and the choice of agents is adjusted based on donor and recipient culture results.

The risk of opportunistic infections is highest in the first 6 months after transplantation. The risk of cytomegalovirus (CMV) infection depends on the serologic status of the donor and the recipient, and seronegative recipients of organs from seropositive donors have the highest risk. Transplant programs use different prophylactic regimens to prevent CMV infection. In a multicenter randomized controlled trial, extended prophylaxis with valganciclovir to 12 months after transplantation was associated with a significantly lower incidence of CMV disease, CMV infection, and disease severity compared to 3 months of prophylaxis (71). Other prophylactic regimens have not been as carefully studied, but most patients are treated with an antibiotic for prophylaxis against *Pneumocystis jirovecii* pneumonia. Recipient-derived infections remain common

in the first 6 months. In addition, community-acquired infections including CARV (e.g., influenza, respiratory syncytial virus, etc.), bacterial pneumonia and endemic fungi (e.g., histoplasmosis, coccidioidomycosis) can be a significant cause of morbidity.

Infections can have an immediate and direct impact on lung transplant recipients resulting in hospitalization and increased health care utilization (72). Furthermore, multiple infections have been associated with an increased risk of CLAD development and progression in the ensuing months after the infection (72–74). Respiratory viral infections have been linked to the development of BOS (73). The development of epithelial fibrosis and luminal obliteration characteristic of OB after viral bronchiolitis is easy to envision. In addition, bacterial respiratory infections including *Staphylococcus aureus* and *Pseudomonas aeruginosa* and fungal colonization with *Aspergillus* species have been linked to CLAD and increased mortality (74–78). The



**Figure 5** Spirometry and imaging studies. (A) Spirometry and imaging studies at the time of diagnosis of BOS are illustrated. The chest X-ray and chest CT scan are clear. (B) Spirometry and imaging studies as chronic lung allograft dysfunction evolved into RAS. The chest X-ray and CT scan illustrate patchy peripheral consolidation, ground glass opacification, and traction bronchiectasis. BOS, bronchiolitis obliterans syndrome; RAS, restrictive allograft syndrome; CT, computed tomography; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 second.

relationship between the isolation of *Pseudomonas aeruginosa* and CLAD is more complex. In a large single center study, *de novo* acquisition of *Pseudomonas aeruginosa* was associated with an increased risk of CLAD, but the persistence of pre-transplant *Pseudomonas aeruginosa* culture positivity post-transplant was not (79). A paradigm for the association between infections and the development of CLAD is that organisms stimulate the release of chemokines from the allograft resulting in the recruitment of leukocytes which further amplify the recruitment of additional inflammatory cells and allograft injury (80). It is also possible that alloimmune responses injure the airway epithelium first, and this increases the risk of infection.

## Conclusions

Lung transplantation is the ultimate treatment for patients with advanced lung disease. Although there have

been significant improvements in survival since lung transplantation became a clinically viable treatment in the 1980s, survival after lung transplantation continues to lag behind survival after other solid organ transplants. Indeed, long-term outcomes remain disappointing in spite of advances in donor and recipient selection and management. Rejection and infection are the leading causes of death after transplantation. This highlights the critical role of the immune response after transplant and underscores the need for better clinical immunosuppression and immune monitoring. Clearly, there are ongoing unmet needs in the management of lung transplant recipients, and future studies are necessary to continue to advance the field and improve patient outcomes.

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## Footnote

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