Review Article

Chronic and long-term complications after lung transplant: a narrative review

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Background: The purpose of this article is to provide a current literature overview of long-term complications after lung transplantation (LT) which commonly affect graft survival. Long-term survival after LT is poor compared to that of other solid organ transplants. Understanding entities which influence graft function will lay a platform for new research into prevention and treatment and hopefully translate to improved survival.

Methods: Narrative overview of literature retrieved from searches of computerized databases (predominantly PubMed from 1990 to 2020) and other authoritative texts. The review focused primarily on terms related to chronic lung allograft dysfunction and infections which most commonly lead to graft failure, with an emphasis on current recommendations.

Results: One-year survival after LT has improved significantly. Median survival worldwide is now 6.2 years (improved from 4.3 in the era 1990–1998) and if recipients survive the first year, median survival is 8.3 years. Median survival worldwide over the period 2009–2016 is 6.5 years. Despite these improvements, long-term survival after LT continues to lag survival after other solid organ transplants. Long-term medical complications after LT are diverse and encompass predominantly events related to infections, chronic rejection, malignancy, or sequelae of large airway complications. Complications related to onset and progression of chronic lung allograft dysfunction (CLAD) translates to poor long-term survival and patients remain at risk for infections throughout their post-transplant lives. Furthermore, infection is often a risk factor for CLAD and vice versa. This review provides a brief overview of these entities.

Conclusions: Long-term complications of infection and chronic graft failure continue to limit survival after LT. The last two decades have cast significant light on the etiology and pathogenesis of chronic graft failure.

Keywords: Chronic lung allograft dysfunction (CLAD); lung transplant; transplantation; chronic graft failure; complications

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Introduction

One-year survival after lung transplantation (LT) has improved significantly. Median survival worldwide is now 6.2 years (improved from 4.3 in the era 1990–1998) and if recipients survive the first year, median survival is 8.3 years. Median survival worldwide over the period 2009–2016 is 6.5 years (1). Despite these improvements, long-term survival after LT continues to lag survival after other solid organ transplants. Long-term medical complications after LT are diverse and encompass predominantly events related to infections, chronic rejection, malignancy, or sequelae of large airway complications (*Table 1*). Complications

Table 1 Potential medical complications after lung transplantation

Infections (bacterial, fungal, viral, mycobacterial, protozoal):
Early (perioperative), subacute, chronic
Rejection:
Acute (perivascular lymphocytic), Chronic (CLAD phenotypes)
Malignancy:
Post-transplant lymphoproliferative disorder, skin cancer, solid tumors (native lung after single lung transplant), colon cancer in cystic fibrosis)
Cardiovascular:
Hypertension, arrhythmia, accelerated coronary artery disease, venous thromboembolism
Renal and electrolytes:
Acute renal insufficiency, chronic kidney disease, hypomagnesemia
Gastrointestinal:
Gastroesophageal reflux, gastroparesis, esophageal motility, cholestasis, biliary dysfunction.
Hematological:
Anemia, leukopenia, thrombocytopenia
Endocrine disorders:
Steroid induced diabetes, dyslipidemia, gonadal dysfunction, obesity
Musculoskeletal:
Osteoporosis, myopathy
Neurological:
Posterior reversible encephalopathy syndrome (PRES), peripheral neuropathy, tremor, memory loss
Drug reactions:
Calcineurin inhibitor toxicity, multiple drug-drug interactions

CLAD, chronic lung allograft dysfunction.

related to onset and progression of chronic lung allograft dysfunction (CLAD) translates to poor long-term survival and patients remain at risk for infections throughout their post-transplant lives. Furthermore, infection is often a risk factor for CLAD and vice versa. This review provides a brief overview of these entities, attempting to address the most poignant clinical issues, highlighting where advances have been made and emphasizing where deficits still exist. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ccts.amegroups.com/article/view/10.21037/ccts-20-174/rc).

Methods

A list of search terms was compiled (*Table 2*) based on clinical experience. PubMed searches were performed using the search term 'lung transplant' and each term. Systematic reviews were separately noted (*Table 2*) and emphasis placed on search results obtained within the last decade for purposes of this review.

Discussion

Infectious complications

Bacterial infections

In contrast to other solid organs, lung transplant itself is a major risk factor for infections (2). Exposure to environmental insults, compromised cough reflex and impaired muco-ciliary clearance in the setting of denervation all contribute to increasing risk of infections (3-5). Furthermore, infection increased the risk of CLAD which in turn has been deemed a major risk factor for subsequent infection (6).

Infection has been identified as the leading cause of death, accounting for 37% of cases between 30 days and 1 year post-lung transplant (7). Bacterial infections are most common, accounting for 35–66% of cases. Most bacterial infections occur in the immediate postoperative period (first 2 weeks) with the vast majority localized to the lungs, mediastinum, or pleural space (8-11). Complicated surgical site infections, including empyema, surgical wound, mediastinitis, sternal osteomyelitis and pericarditis occur in approximately 5% of patients within the first month, with a mean onset 25 days post-transplant and may contribute significantly to decrease in 1 year survival. Pleural space infections occur in up to 27% of cases with *Candida albicans* being the most frequent culprit (12). Methicillin resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* (PsA) and other gram-negative bacteria predominate in the first 6 months, with *Nocardia* sp., *Listeria* and *Pneumocystis Jirovecii* occurring occasionally during this period (2). Pneumonia is the most common presenting infectious clinical manifestation after lung transplant. In the early period (<30 days), health care associated pathogens PsA (33%), MRSA (26%), *Acinetobacter* (16%) and *Aspergillus* sp. predominate, while community acquired pathogens *S. Pneumoniae*, *Legionella* and viral infections are the most

Table 2 Long-term complications commonly affecting lung allograft function

PubMed search term: "lung transplant" + term below	Search 1/1/1990 to 11/6/2020	Systematic review 1/1/1990 to 11/6/2020	Search 11/6/2010 to 11/6/2020	Systematic review 11/6/2010 to 11/6/2020
Infection				
Bacterial				
Pseudomonas sp.	n=507	n=0	n=263	n=0
Staphylococcus aureus	n=188	n=0	n=101	n=0
Acinetobacter	n=38	n=0	n=31	n=0
Nocardia	n=138	n=0	n=55	n=0
Mycobacteria	n=356	n=2	n=216	n=2
Viral				
Cytomegalovirus (CMV)	n=1486	n=8	n=377	n=5
Epstein Barr virus (EBV)	n=363	n=1	n=135	n=1
Respiratory viruses	n=773	n=8	n=485	n=8
Fungal				
Aspergillus sp.	n=776	n=4	n=311	n=4
Scedosporium sp.	n=87	n=0	n=51	n=0
Chronic rejection				
Chronic lung allograft dysfunction	n=885	n=7	n=649	n=7
Bronchiolitis obliterans syndrome	n=2555	n=15	n=708	n=9
Restrictive allograft syndrome	n=127	n=1	n=119	n=1
Neutrophil reversible allograft dysfunction	n=17	n=0	n=10	n=0
Airway complications				
Bronchial stenosis	Not reviewed	–	–	–
Bronchomalacia	–	–	–	–

frequent culprits beyond 6 months (13).

Bacterial infections portend a lower mortality than fungal or viral infections but in terms of actual numbers, account for more total deaths (14,15). Data on outcomes secondary to bacterial colonization is contradictory. Shteinberg *et al.* reported a relative risk for mortality of 9.2% in LT recipients colonized with fluoroquinolone resistant gram-negative bacilli (16). Others have reported that colonization with multi-drug resistant or pan-resistant organisms does not increase risk of infection or impact survival (17,18).

Genetic factors may affect outcome. Toll-like receptor 4 (TLR4) polymorphisms associated with endotoxin hypo-responsiveness have been linked to significantly lower risk for acute rejection in the first 3 years and a trend towards decreased onset of grade 2 or 3 CLAD. Genetic deficiency of pentraxin 3 (PTX3), a soluble pattern recognition receptor, is known to effect tuberculosis and PsA colonization in patients with cystic fibrosis (CF), and predispose to invasive aspergillosis (19).

Special considerations

Patients with CF colonized with PsA, MRSA or *Aspergillus* sp. are not at greater risk for infectious complications than non CF patients (9). *Burkholderia Cepacia* complex and in particular genotype *Cenocepacia* has been deemed an absolute contraindication to transplantation at some centers due to poor outcomes reported in earlier series(20). However, single center reports of equivalent outcomes have recently challenged this paradigm (21).

Mycobacterial infections appear to be on the rise. *Mycobacterium Abscessus* is of particular concern and may

cause disseminated disease. Skin lesions are the most common clinical presentation in solid organ transplantation, but in lung transplant recipients, pleuro-parenchymal disease is more common. Most centers recommend initiating therapy for non-tuberculous mycobacterial disease pre-transplant if clinical and radiographic findings suggest active infection (22).

Nocardia frequently occurs in the native structurally damaged lung of single lung transplant recipients. Infection with Nocardia, while rare (0.6–2.1%) carries increased mortality (up to 75%) in lung transplant recipients with *N. farcinica* being a particularly virulent strain. Trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis does not necessarily preclude the diagnosis since TMX-SMX resistant strains exist. Nocardia notoriously mimics other pathogens and should be considered in all cases of pneumonia not responding to conventional antibiotics (23,24).

Viral infections

Respiratory viruses, herpesvirus infections, hepatitis viruses, polyomaviruses and parvovirus require attention in this population group. This review will focus on viruses that are most likely to affect allograft function (25).

Respiratory viruses

Respiratory viral infections often lead to an ominous course in lung transplant recipients and may precipitate a permanent decline in lung function, either directly or as a precipitant to chronic rejection. Most common culprits belong to the families Orthomyxoviridae (influenza A & B), Paramyxoviridae (respiratory syncytial virus/RSV, parainfluenza, human metapneumovirus), picorna viruses (rhinovirus, enterovirus) and adenovirus (26,27). Additionally, the impact of the recent SARS corona virus (SARS CoV) pandemic on lung transplant recipients requires attention. SARS CoV is addressed in a separate chapter. Respiratory virus infections can occur at any time after transplant or be transmitted from donor organs.

Immunosuppression may significantly prolong the clinical course. Rhinovirus particles have been recovered 15 months after the initial infection in LT recipients (28). The yield of recovering virus/viral particles is significantly higher in symptomatic (34–66%) than asymptomatic individuals (3–5%). In pediatric transplant recipients, younger age is associated with increased risk, but in the adults, neither age, type of transplant or underlying diagnosis appear to increase risk (25,29,30). Controversy exists regarding respiratory viral infections as a potential precipitant for acute cellular rejection (ACR). One study suggests an association, whereas several others (albeit with significant design flaws) do not (29,31-33). However, there appears to be a strong epidemiological link between viral infection and development of chronic rejection/CLAD. Retrospective studies suggest subsequent CLAD development in up to 60% of cases following a community acquired respiratory virus (CARV) infection, with infection in the first year carrying additional long-term increased risk (29,34,35). Limited data suggests that "non-rhinovirus" infection and RSV appear to have an increased association with development of CLAD compared to human metapneumovirus (36,37).

Treatment of respiratory viral infections depends on etiology. Early intervention for influenza following current guidelines shows clear benefit in terms of outcomes (38). Treatment options for RSV include ribavirin (oral, intravenous, or inhaled) with or without incremental steroid doses and intravenous immunoglobulin (IVIG) (39). Data supporting this approach stems from case series. Li *et al.* evaluated 21 cases comparing oral (n=6) *vs.* inhaled ribavirin (n=21). This retrospective study showed no difference in outcomes between inhaled or oral ribavirin groups at 6 months post infection (40). Observational studies with RSV-specific humanized monoclonal antibody, Palivizumab suggest that it is well tolerated in lung transplant recipients albeit without any reduction in severity of illness or mortality benefits (41). Treatment of RSV infection with ALN-RSV01, a small interfering RNA, administered as inhalation therapy which targets viral replication has shown a trend towards a decrease in new or progressive bronchiolitis obliterans syndrome (BOS). Treatment efficacy was enhanced when therapy was started within 5 days of symptom onset (42). Limited data suggests successful treatment of Adenovirus infection with Cidofovir and IVIG (43). Rhinovirus, the most frequently isolated respiratory virus in lung transplant recipients, does not currently have any effective treatment options.

Herpesviridae

The herpesviridae family of viruses, including cytomegalovirus (CMV) and Epstein Barr virus (EBV) are the most commonly associated viruses causing infection related complications after LT. Infection can occur by donor transmission, reactivation, or primary natural infection. CMV or EBV donor sero-positive to recipient CMV or EBV sero-negative recipients are at significantly higher risk than seropositive recipients. CMV pneumonitis is a major risk factor for onset of CLAD while EBV viremia carries risk for development of post-transplant lymphoproliferative disorder.

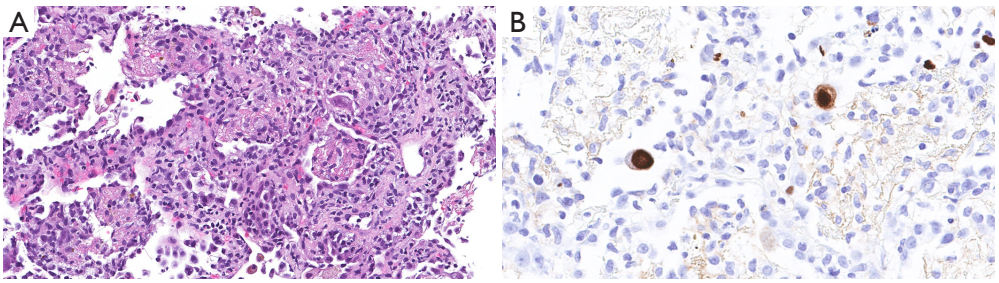

Figure 1 CMV pneumonia. (A) CMV pneumonia with alveolar septal thickening and intraalveolar fibrin balls (HE stain, original magnification ×200); (B) immunohistochemistry reveals nuclear CMV inclusions (original magnification ×400). CMV, cytomegalovirus.

CMV

CMV infection is defined as replication of virus detectable by nucleic acid testing or antigenemia regardless of symptoms, whereas CMV disease implies infection with attributable symptoms (*Figure 1*). The main risk factors for CMV disease relate to donor-recipient serostatus (D+/R–), induction immunosuppression with lymphocyte depleting agents and enhanced immunosuppression to treat acute rejection episodes (44). The incidence of CMV disease in lung transplant recipients varies from 5% to 40% (44-46). CMV disease incidence is higher in lung transplant recipients compared to other solid organ recipients. However, in the current era of routine CMV prophylaxis, the incidence of CMV pneumonia is low. In two prospective cohorts, CMV replication in allografts [measured by polymerase chain reaction (PCR)] was 41% and 44% at 1 year, however, pneumonitis developed in only 5–8% (47,48). Due to improved treatment and preventive strategies, mortality from CMV is rare. A significant concern in lung transplant recipients with CMV infection, is the potential for development of CLAD (45). CMV has been identified as a significant risk factor for CLAD in an Australian study (HR =2.1, P=0.003) (48). A Swedish study demonstrated that both CMV disease and CMV infection resulted in lower BOS-free survival (32% and 36%) *vs.* 69% in patients without CMV infection (49).

The optimal length of antiviral prophylaxis is unknown, but most studies have demonstrated prophylaxis less than 6 months to be associated with an increased incidence of CMV disease (50). A randomized trial comparing CMV prophylaxis for 3 months to 12 months revealed incidence of CMV disease was 32% *vs.* 4% respectively (P<0.001) (49). Notwithstanding, a duration of at least 6 months prophylaxis for the intermediate risk group (D–/R+) appears to be adequate (50). Some centers have employed a combination of CMV specific IVIG in addition to anti-viral drug prophylaxis. This approach has not yet been validated to provide additional benefit. Our lung transplant group favors prophylaxis for a minimum 6 months in the intermediate group (R+) and lifelong in the high-risk group (D+/R–). We discontinue prophylaxis in the latter group if seroconversion to R+ occurs after the first year.

Therapeutically, oral valganciclovir has good bioavailability, providing adequate treatment for mild to moderate disease, but IV ganciclovir is preferred for severe cases with end-organ involvement. Following treatment, subsequent prophylaxis is generally recommended for 4 to 8 weeks to prevent relapse (51,52). Lung transplant patients are also at high risk of antiviral resistance. Most mutations coding for antiviral resistance reside in UL97 kinase or UL 54 polymerase. UL 97 resistance can usually be overcome by increasing the dose of ganciclovir, while UL 54 mutations require alternative antiviral treatment, typically with Foscarnet. Newer antiviral agents, letermovir and brincidofovir have not been fully evaluated in lung transplant recipients. Letermovir has recently been approved for CMV prophylaxis after hematopoietic stem cell transplantation. Veit *et al.* recently reported successful rescue therapy with Letermovir in 4 lung transplant recipients who were failing conventional therapy (53). The oral agent brincidofovir has demonstrated anti-CMV activity with decreased overall CMV DNAemia in post-hematopoietic stem cell transplant recipients, but failed to decrease clinically significant disease or DNAemia in a recent phase 3 trial (54). The mTOR inhibitor, sirolimus has a theoretical antiviral advantage compared to other immunosuppressants. In kidney transplant recipients, substitution of sirolimus for mycophenolate has been successfully employed in patients suffering recurrent CMV viremia without provoking rejection (55).

EBV

EBV is a Herpesvirus that infects more than 95% of the

world's population, predominantly children and young adults. Infection frequently is asymptomatic but may manifest as a viral syndrome with adenopathy and fever (infectious mononucleosis). Post-transplant primary infections range from an infectious mononucleosis type syndrome (more common in children) to monoclonal lymphocyte proliferation and possible high-grade lymphoma (56). Post-transplant lymphoproliferative disorder (PTLD) is on this spectrum of disorders and occurs due to lack of surveillance of EBV infected B-lymphocytes due to immunosuppression. Lymphocyte depleting induction agents typically increase the risk, especially in seropositive donors to seronegative recipients (D+/R–) (57). The m-TOR inhibitor sirolimus protects against proliferation of EBV infected cells in animal models and may play a protective role in transplant recipients (58,59). Some centers have employed ganciclovir prophylaxis in high risk EBV mismatch (D+/R–) cases based on in-vitro activity against EBV. However, agents such as acyclovir or ganciclovir act only on lytic virus and have no activity against latently infected B cells and are hence ineffective for treatment of EBV DNAemia (61). Since these patients are at highest risk of developing PTLD, they would intuitively be potential candidates for a reduction in immunosuppression, possible antiviral or anti-lymphocyte B-cytotoxic therapy (56). Administration of the anti-CD20 monoclonal antibody rituximab has been shown to be effective in controlling EBV DNAemia and PTLD in patients undergoing allogeneic hematopoietic stem cell transplants (HSCT) (61). Simply lowering immunosuppression in pediatric liver transplant recipients with EBV DNAemia has been shown to result in significantly lower PTLD (62). Some groups have shown efficacy in lowering EBV DNAemia by administering autologous or allogeneic EBV-specific cytotoxic T cells after HSCT after lowering immunosuppression had proven ineffective. This strategy, however, has not been effective after solid organ transplantation (60).

In summary, treatment of EBV related PTLD still requires reduction of immunosuppression as a first step, followed by therapy with rituximab or chemotherapy if ineffective or in cases of aggressive PTLD. (56) EBV specific cytotoxic T-cell infusions can be tried if there is no response to other measures.

Mold infection

Mold accounts for approximately 70% of invasive fungal infections after lung transplant and the cumulative risk in the first year after transplant is 8.6%. LT recipients are at increased risk of mold infections due to direct environmental exposure, impaired mucociliary clearance, denervation and colonization of the airway or native lung after single LT (63). *Aspergillus* and *Scedosporium* spp. account for up to 73% and 27% of these infections respectively. Factors associated with increased risk include increased immunosuppression, neutropenia, anti-lymphocyte induction (particularly OKT3), prior CMV infection, single LT, environmental exposures such as farming, gardening, composting, marijuana smoking and known airway colonization pre-transplant.

Aspergillus

Aspergillus is the most common cause of invasive fungal infection (IFI) after LT. Predisposing factors are noted above. The association between CMV infection and invasive aspergillosis (IA) has been well documented but the mechanism remains unclear. Pre-transplant colonization with *Aspergillus* sp. increases the risk of IA fourfold post-transplant. In patients who have undergone stem cell transplant, genetic deficiency of PTX3, a soluble pattern recognition receptor, has been found to increase the risk of both CMV and Aspergillosis. Of note, 60% of patient with CF, one of the significant etiologies for end stage lung disease requiring LT, may be colonized with *Aspergillus* sp. (62,64).

Aspergillus may present with diverse clinical presentations. These include colonization (up to 46%), tracheabronchitis (<1%), invasive pulmonary aspergillosis (IPA) or disseminated disease. Colonization usually develops within the first 3 months after transplant. This presentation typically represents a benign course. However, without appropriate prophylaxis there is an 11-fold increase for subsequent IPA. CLAD has also been associated with colonization with conidia producing (<3.5 μm) species (*A. fumigatus*, *A. nidulans*, *A. terreus*, *A. flavipes*) (65-67). Tracheobronchitis from aspergillosis is rare. It has a median onset 2.7 months post-transplant. The diagnosis can be confounded by presence of ischemic necrosis, especially when it occurs close to the bronchial anastomotic line (68,69). The clinical presentation includes ulcers, necrosis, or pseudo-membranes in the presence of positive microbiology. Outcomes are generally favorable, but occasionally lead to airway stenosis, bronchial dehiscence, bronchopleural fistulas, or fatal hemorrhage (69). IA accounts for 93% of IFI, with a median onset 10.5 months post-transplant. Patients may present with dyspnea (65%), cough (58%) and sputum production (42%). Less than one third of cases present with fever. Occasionally, patients present with pleuritic chest pain or hemoptysis due to infarction (64). Disseminated disease occurs in

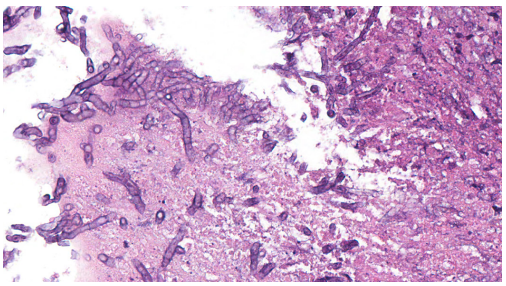

Figure 2 Bronchial wall with necrosis and fungal organisms, consistent with Aspergillus species (HE stain, ×200).

approximately 4% of cases. Dissemination occurs most commonly to skin, the gastrointestinal tract, endovascular (including endocarditis) or bone. Central Nervous System (CNS) dissemination portends a poor prognosis (70).

The distinction between colonization and infection poses diagnostic challenges. The European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) has attempted to standardize definitions of IFI for research and clinical trials. They have proposed "proven", "possible" and "probable" categories. Proven IFI requires histopathological identification of an invasive fungal infection or positive culture from a normally sterile site. Probable IFI require host factors and presence of radiological or mycological criteria. Those who do not meet the mycological criteria are considered "possible IFI".

Mycological criteria include mold recovered by culture, detection of microscopic fungal elements or galactomannan antigen, aspergillus antigen in plasma, bronchoalveolar lavage (BAL) or cerebrospinal fluid (CSF), or PCR positive testing at similar sites (*Figure 2*). Newer PCR assays are useful to detect species of Aspergillus as well as mutations associated with azole resistance (71). Classic radiological criteria for IA include dense well circumscribed lesions ± a halo sign (nodular mass surrounded by ground-glass opacity caused by localized infarction) or cavitation on CT (72). The International Society for Heart and Lung Transplantation (ISHLT) has also published definitions for IFI in lung transplant recipients (69). Plain chest X-ray is neither sensitive nor specific to detect pulmonary infection in the lung transplant population group. Furthermore, the "halo sign" is seldom seen in non-neutropenic solid organ transplant recipients. In patients with proven or probable IFI, bronchial wall thickening and centrilobular opacities with tree-in-bud are the most common findings (73).

Treatment, as for other infections, should be two-pronged, including reduction in IS and addition or escalation of antifungal therapy. Attention should be paid to special circumstances, for instance tracheobronchial aspergillosis (TBA) requires inhaled and systemic antifungal therapy. Anastomotic dehiscence may require stent placement and/or surgical intervention. Voriconazole remains the first line therapy for IA, providing better results than conventional amphotericin B both in response rate (53% *vs.* 32%) and lower mortality rate (29 *vs.* 42%) (74). Amphotericin B and its lipid formulations are considered "alternative" treatments for IA. Voriconazole is notorious for drug-drug interactions due to its effect at cytochrome p450 2C19, CYP 2C9 and CYP34A. Most common side-effects include visual disturbances (20%), hepatic dysfunction (12–20%) and photosensitivity. The echinocandins (caspofungin, anidulafungin and micafungin) also demonstrate activity against aspergillus. At our center, we will consider adding caspofungin to voriconazole in severe cases of IA. Posaconazole has excellent *in vitro* activity and a favorable safety profile but also interacts with CYP34A, necessitating careful surveillance for drug-drug interactions (75). Prophylactic regimens vary. At our center, we use a combination of echinocandin (caspofungin) and inhaled amphotericin prophylaxis early after transplant and transition to oral itraconazole, reserving voriconazole and posaconazole for treatment of infections due to their higher incidence of side effects.

Scedosporium

Overall, the four ubiquitous species of Scedosporium, *S. apiospermum*, *S. boydii*, *S. aurantiacum* and *S. prolificans* account for up to 27% of mold infections after LT, with a median occurrence 12 months after transplant. Colonization occurs in 8% of patients with CF, increasing the risk of invasive disease in this population group (76,77). Clinical presentations include colonization, sinopulmonary disease, mycetoma and disseminated disease with central nervous system involvement. Almost 50% develop disseminated disease. The radiographic and histopathological findings are indistinguishable from aspergillus, but with higher relapse rates and higher resistance to antifungal therapy (77). Scedosporium is inherently resistant to amphotericin B, with variable resistance to itraconazole, posaconazole, voriconazole and micafungin. Voriconazole is the agent most active against *Scedosporium* sp., either alone or in combination (78). *S. prolificans* is particularly resistant. The combination of voriconazole and terbinafine has proven successful in

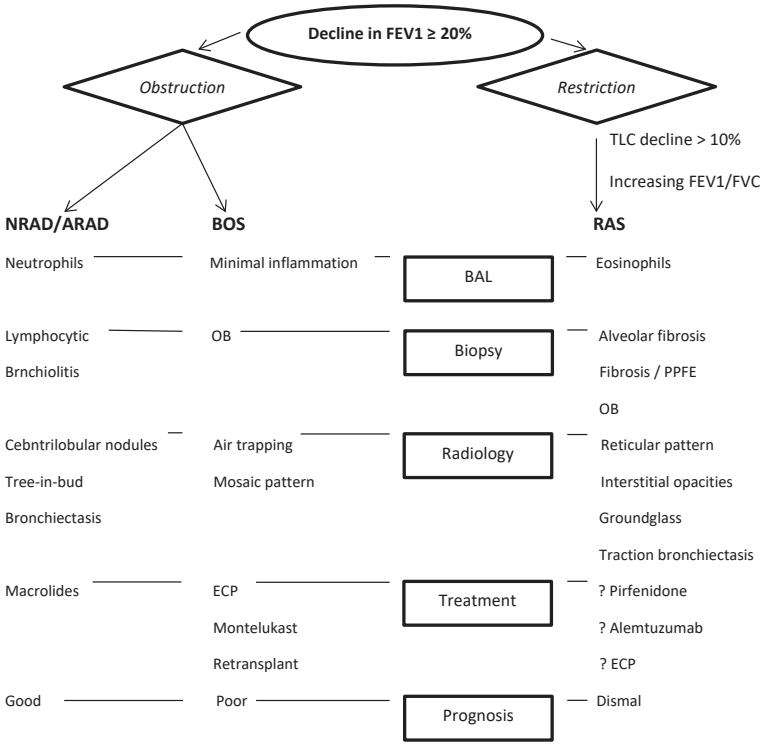

Figure 3 CLAD phenotypes. CLAD, chronic lung allograft dysfunction; FEV1, forced expiratory volume in 1 second; NRAD, neutrophil reversible allograft dysfunction; ARAD, azithromycin reversible allograft dysfunction; BOS, bronchiolitis obliterans syndrome; ECP, extracorporeal photopheresis; TLC, total lung capacity; FVC, forced vital capacity; RAS, restrictive allograft syndrome; BAL, bronchoalveolar lavage; OB, obliterative bronchiolitis; PPFE, pleuroparenchymal fibroelastosis.

treating a case presenting with brain abscess (79). Overall prognosis is poor, especially with dissemination, with reported mortality ranging 54–78% (80).

Although infrequent, lung transplant recipients are also at risk for a variety of other mold infections, including dematiaceous molds, Zygomycosis (previously called mucormycosis), and endemic mycosis (histoplasmosis, blastomycosis and coccidiomycosis) which may be prevalent in certain geographic zones. Additionally, yeast infections, particularly *Candida* sp. are responsible for 23% of all invasive fungal infections (81).

CLAD

The true incidence of CLAD is unknown considering inconsistencies of definitions over different time periods, selection bias in reported mortality from single centers, and cause of death being defined as 'graft failure' *vs.* BOS in registries. Although one -year survival has improved steadily over the past 2 decades, improvement in long-term survival after LT has not followed suit (82). CLAD remains the most significant barrier to long-term survival after LT. BOS and restrictive allograft syndrome (RAS), representing obstructive and restrictive pathophysiology respectively, are now widely accepted clinical phenotypes falling under the umbrella term 'CLAD'. Most studies predate separation of CLAD into phenotypes. Additionally, the entity of neutrophil reversible allograft dysfunction (NRAD), also termed azithromycin responsive allograft dysfunction (ARAD) has been separately defined under the CLAD umbrella (*Figure 3*) (83,84). Frequently, patients may present with features of predominantly one or a combination of these phenotypes. CLAD staging is based on decline in FEV1, which applies to both BOS and RAS (85). For the purposes of discussion, we will discuss each phenotype separately.

BOS phenotype

BOS after LT is the surrogate term for the clinical entity representing the underlying pathological finding

of bronchiolitis obliterans (BO or OB). Clinically, the diagnosis requires at least a 20% decline in FEV1 compared to the mean of the 2 best FEV1 values (taken at least 3 weeks apart) after transplant (*Table 3*). It also requires exclusion of confounding factors such as infection, acute rejection, large airway complications or recurrent native disease. The pathogenesis of BOS is still poorly understood and mortality is high (*Figure 4A*) (86).

Clinical factors associated with a higher risk for rapid decline include female sex, underlying diagnosis of IPF and single LT. Onset within the first 3 months is associated with particularly poor survival (87,88). Prominent risk factors for BOS include allo-immune factors, primary graft dysfunction, gastro-esophageal reflux disease (GERD), infection, BAL neutrophilia (16–24% threshold), single *vs.* bilateral LT (49% *vs.* 32% respectively in a review of 225 patients) and medication non-compliance (89-91).

BOS is commonly associated with the severity of acute rejection episodes, either perivascular (grade A) or peri-bronchiolar (grade B). Grade A2 or higher rejection episodes correlate well with development of BOS in many studies (92-94). Recurrent A1 rejection episodes may also predict the syndrome, a finding which has therapeutic implications (95). Lymphocytic bronchiolitis or grade B rejection is also cited as a risk factor for development of BOS. Consequently, treatment of greater than minimal risk (grade A or B) acute rejection remains uncontroversial due to a strong link between ≥ A2 rejection with BOS. Over the past two decades, ISHLT, ERS, and ATS guidelines have instituted guidelines which recommend treatment of clinically significant A1 rejection (96,97).

Pathophysiologically, animal studies (and limited human studies) suggest sensitization may take place due to exposure of collagen V in epithelium of small airways. Auto-antibodies to Kα1-tubulin has also been linked to the pro-fibrotic process of BO (98,99). Other risk factors with a strong correlation include GERD (both acid and non-acid reflux) (92,93) and viral infections, particularly CMV which can also cause BO in a non-transplant setting. CMV pneumonitis in the first 6 months portends a poor prognosis in terms of BOS onset and mortality (100). Community acquired respiratory virus infections (particularly RSV and influenza), bacterial respiratory infections, especially Pseudomonas sp. and aspergillus infections have all been linked to development BOS (25,26,31,66,101).

Several potential surrogate markers for BOS have been studied but so far, but none have proved superior to pulmonary function testing. BAL parameters associated with pro-inflammatory state (IL-8, neutrophilia, chemokine monocyte chemoattractant protein 1/MCP-1), markers of innate immunity (alpha defensins), enzymes linked to neutrophil migration and extracellular matrix remodeling (matrix metalloproteinase/MMP-9) and markers of oxidative stress (myeloperoxidase and glutathione) have all

Table 3 CLAD: severity for BOS or RAS

CLAD grade	FEV1 % of baseline
0	>90% and $FEF_{25–75\%}$ >75%
0-p	81–90% and $FEF_{25–75\%}$ <75%
1	66–80%
2	51–65%
3	≤50%

Data from Verleden *et al.* (85). CLAD, chronic lung allograft dysfunction; BOS, bronchiolitis obliterans syndrome; RAS, Restrictive allograft syndrome; FEV1, forced expiratory volume in 1 second.

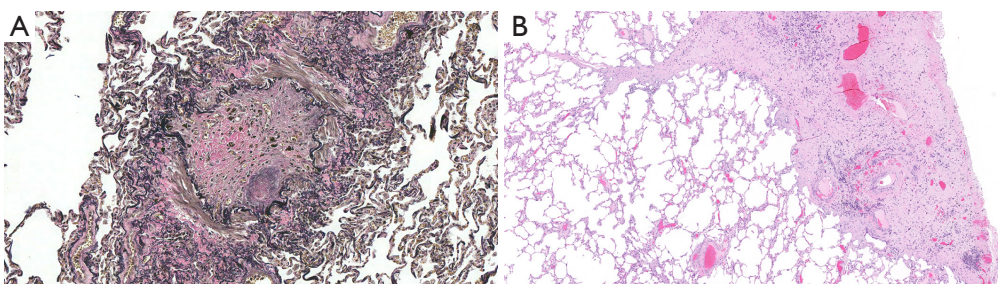

Figure 4 Histopathologic correlates of CLAD. (A) Obliterative bronchiolitis. The lumen of a bronchiole is completely obliterated by scar tissue and can only be recognized by a Verhoeff-Van Gieson stain, which highlights its elastic layer (×100). (B) Pleuro-parenchymal fibroelastosis showing subpleural elastotic fibrosis with abrupt transition to the unaffected alveolated parenchyma (HE stain, ×20). CLAD, chronic lung allograft dysfunction.

been implicated in the development of BOS (102-107).

Diagnosis by CT has gained traction, particularly after pediatric LT, where lung function testing may be less reliable. Typical findings on CT scan imaging include air-trapping on expiratory images, bronchiectasis, and a mosaic pattern. Although air-trapping correlates more strongly with BOS than other CT findings, this finding is not sufficiently accurate to predict onset of BOS before spirometry (108-112).

The therapeutic landscape for medical management of BOS is relatively barren. There is no clear evidence to suggest that any particular immunosuppressive regimen is superior for BOS prevention. High dose steroids (>30 mg daily prednisone) are also not recommended due to significant side-effects and lack of superior outcomes. Most centers will switch cyclosporine to tacrolimus if relevant, due to a clinical trial showing slower progression of BOS with tacrolimus (113). Adding macrolides for anti-inflammatory effect may be beneficial for both preventing or treating BOS, particularly in patients with neutrophil predominant disease characterized by BAL neutrophilia >15% and associated peri-bronchial infiltrates with tree-in bud appearance (114,115). Our group favors starting azithromycin 250 mg three times a week for CLAD prophylaxis early after LT.

All patients with BOS should be evaluated for GERD. Recommendations for gastric fundoplication after transplant are based on several studies in patients with GERD and BOS which identified GERD as a risk factor (116,117). Early fundoplication (<3 months post lung transplant) has been associated with freedom from BOS and improved 1- and 3-year survival (118,119). Complications of bleeding, gastric perforations and dysphagia have been reported in 5–25% of patients after fundoplication. The optimal timing and patient selection require careful consideration (119).

Patients with scleroderma, a connective tissue disease that can result in pulmonary pathology necessitating LT, require special consideration. This disease affects the proximal gastrointestinal tract in 90% of cases (120). Esophageal dysfunction, delayed gastric emptying and GERD with micro-aspiration increases the risk of BOS. Esophageal dysfunction may increase the risk or contraindicate Nissen fundoplication due to risk of anterograde emptying of the esophagus. Some scleroderma patients may be amenable to Dor (partial) fundoplication while some centers employ Roux-en-Y bypass for reflux control. Despite these limitations, patients with scleroderma appear to have similar outcomes after LT (121,122).

Enhanced immunosuppression strategies using lymphocyte depleting agents alemtuzumab, thymoglobulin or total lymphoid irradiation have suggested benefit by reducing the rate of decline of FEV1 in patients with BOS, but these findings have not been pursued in prospective clinical trials (123-127). Extracorporeal photopheresis (ECP) incubates a patient's peripheral blood monocytes with 8-methoxypsoralen, irradiates the cells, and reinfuses them into the patient. This treatment has an immunomodulatory effect on peripheral blood monocytes and has been associated with a decrease in decline of lung function in patients with BOS. Patients with refractory BOS who stabilized after ECP have been shown to have higher levels of $CD4^+CD25^+$ regulatory T cells than those who were unresponsive, suggesting a mechanism whereby this therapy may work (128). Studies with ECP in BOS have shown an increase in anti-inflammatory and decrease in pro-inflammatory cytokines. Several non-randomized or retrospective studies have suggested clinical and physiologic benefit, but good quality randomized controlled trials are lacking (129). Our program employs a treatment trial of ECP for onset of mild CLAD. A recent trial of montelukast, a cysteinyl-leukotriene type 1 receptor antagonist, administered to 153 patients (115 with BOS and 38 with RAS) showed significant attenuation in rate of FEV1 decline after 3 and 6 months ($P<0.0001$) and this translated to better progression free ($P<0.0001$) and overall survival ($P=0.0002$) (130).

Re-transplantation is a last resort. Selected patients may have good outcomes. Overall, survival after re-transplantation is inferior to primary LT. Survival at one year is approximately 60–78%, with median survival over the past 2 decades of approximately only 2 years. The primary reason for mortality in these patients relates to infection in a retained allograft. For this reason, we suggest re-transplanting the rejected allograft or bilateral lung re-transplantation (131,132).

RAS

In a 1985 report, lung specimens were obtained from 5 heart-lung recipients (2 by autopsy, 2 by open lung biopsy and 1 by re-transplantation). Pathology revealed extensive bronchiolitis obliterans, interstitial, and pleural fibrosis, and accelerated arterial and venous arteriosclerosis. At the time, the conclusion was that BO may be associated with heart-LT. Little was made of the fibrotic changes (133). Similarly, in 2006, a study revealed varying degrees of BO as well as interstitial fibrosis in 2 of 12 patients from specimens obtained at re-transplantation (134). Pakhale *et al.* studied

a 1990 to 2002 cohort of 686 patients from Duke and Toronto. They discovered upper lobe fibrosis in 13 of 686 patients (1.9%) as a novel presentation of chronic allograft dysfunction in lung transplant recipients, differentiated from BOS based on physiologic and radiologic findings.

The restricted phenotype (TLC decline of ≥10%, in addition to FEV1 decline of ≥20%) with associated pleuroparenchymal radiographic changes were found to have a poor prognosis (*Figure 4B*) compared to the predominantly obstructive phenotype without radiographic changes (135,136). Some reports describing RAS have not routinely used TLC, but rather simultaneous FEV1 and FVC decline to define restriction, but with similar poor survival (8 *vs.* 36 months). The most common radiographic findings include interstitial opacities, traction bronchiectasis, architectural distortion and ground-glass opacities (136). Micro-CT (2 mm cuts) and matched histopathology has shown RAS to be associated with greater destruction of both pre-terminal and terminal bronchioles. Also, the interstitial compartments expand and alveolar airspaces are obliterated by accumulation of fibrous connective tissue (83).

Risk factors for RAS remain elusive. Colonization and pseudomonas infection, BAL neutrophilia, lymphocytic bronchiolitis and significant (≥ A2) rejection episodes appear common to both RAS and BOS. However, lymphocytic bronchiolitis (P=0.031) and BAL eosinophilia (≥2%) appear more strongly associated with RAS (137). Differential regulation of cytokines including interleukin (IL)-1beta (P<0.01), IL-1Ralpha (P<0.001), IL-6 (P<0.001), IL-8/CXCL8 (P<0.001), IP-10/CXCL10 (P<0.05), MCP-1/CCL2 (P<0.05), macrophage inflammatory protein (MIP)-1alpha/CCL3 (P<0.001), MIP-1beta/CCL4, and vascular endothelial growth factor (VEGF; P<0.05) have also been implicated in RAS (138).

Treatment options are limited. There are reports of measured success using ECP. A subset of patients with higher BAL neutrophilia and RAS may have a better response with ECP (139,140). Pirfenidone, an antifibrotic agent influencing production of transforming growth factor β (TGF-β) may attenuate the decline in lung function. Translation of the physiologic benefit to clinical improvement, however, warrants further investigation (141). The CD52 antagonist, alemtuzumab, has been utilized with some success in case reports and small series of CLAD patients with rapid decline in lung function. Randomized trials are needed to better establish efficacy and safety (142,143). Patients with RAS suffer far worse 1- and 3-year survival rates (HR =2.6) following re-transplantation compared to BOS patients (144). The decision to re-transplant these patients should be critically discussed, especially when other risk factors are present.

NRAD, later renamed ARAD, encompasses a subset of patients diagnosed with CLAD who show exquisite sensitivity to macrolide therapy, some improving dramatically to no longer meeting criteria for CLAD (145).

This phenotype presents with high BAL neutrophils (>20%), decline in FEV1 of at least 10%, coarse crackles on physical exam, increased sputum production, and with tree-in-bud, centrilobular nodules and bronchiectasis on chest CT. The pathology of ARAD is not fully known. There are pathologic and immunologic similarities between lymphocytic bronchiolitis and ARAD. Both conditions have BAL neutrophilia and lymphocytic inflammation on biopsy and both are poorly responsive to steroid therapy (146).

Conclusions

Despite the minefield of possible complications after LT, outcomes and prognosis for 1-year survival have improved spectacularly over the past 2 decades. The greatest future challenge will be to improve long-term survival. Success in this area will rely heavily on our ability to prevent or treat CLAD.

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