

Chapter 15

Lung Transplantation

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Introduction

Lung transplantation is the only definitive treatment for end-stage interstitial lung disease (ILD). Experience with lung transplantation for patients with classic DC is limited, primarily consisting of case reports in individuals who have previously undergone hematopoietic cell transplant (HCT) [1]. As with lung transplantation following HCT for other causes (e.g., pulmonary graft-versus host disease), careful selection of affected individuals including consideration of infectious risk and other HCT or DC-related organ dysfunction is necessary to achieve successful outcomes [2].

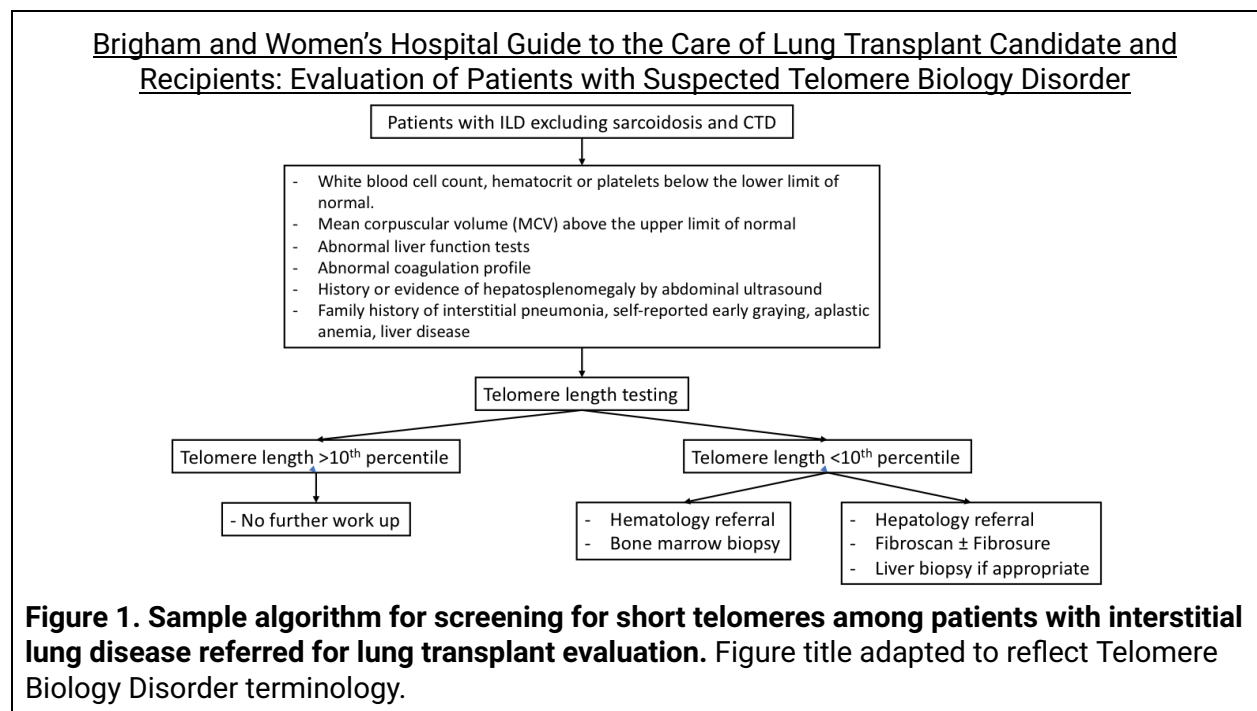
There is, however, a growing literature regarding lung transplantation among adults with short telomere-related ILD. Individuals with ILD and short telomeres with or without known telomere biology disorder (TBD) due to pathogenic germline variants in TBD-associated genes are at risk for more rapid disease progression and decreased transplant-free survival compared to those with normal telomere lengths [3, 4]. Patients and providers should consider early referral to a lung transplant center to begin the evaluation process. Even for individuals who are currently too well for listing, having completed the transplant evaluation can create a safety net in the event of rapid disease progression requiring urgent listing.

Transplant Evaluation

Despite a growing awareness of the role of short telomeres in pulmonary fibrosis, the majority of patients with ILD who are referred to a lung transplant center will not have been screened for short telomeres. We recommend screening for telomere length in individuals with a personal history of early graying (before 30 years old), cytopenias (low blood cell counts) or macrocytosis (large red blood cells), and/or abnormal liver function tests or imaging suggestive of hepatic impairment without other explanation; or with a family history of one or more first degree relatives with ILD. Figure 1 and Figure 2 illustrate two potential screening protocols. Additional assessment, including evaluation for TBD-related mutations, should occur in close collaboration with medical genetics clinicians and genetic counselors.

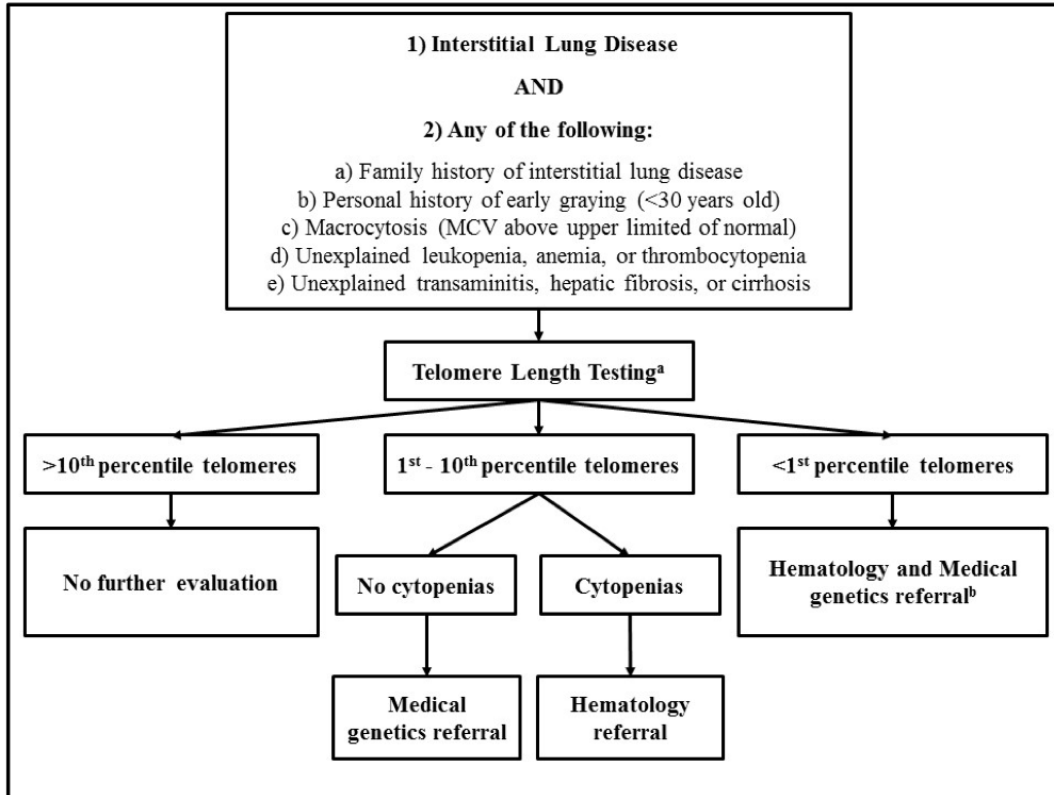
Importantly, the goal of telomere length screening is not to identify a contraindication to lung transplantation. In our opinion, it is important to identify candidates with short telomeres so as to stratify their risk for extra-pulmonary disease manifestations and to design appropriate post-transplant management strategies to allow successful

transplantation. For example, early case series suggested that lung transplant recipients with short telomeres were more likely to have hematologic complications [5, 6]. Because of the risk of bone marrow failure, two authors (SEC and DH), recommend routine bone marrow biopsy as part of the lung transplant evaluation for all patients with short telomeres (<10th percentile for age) [6] (Figure 1). Other programs, however, only proceed with bone marrow biopsy in the presence of significant cytopenias in one or more cell lines. For potential candidates with severe hypocellular bone marrow without malignant transformation, consideration should be given to referral to a center that can offer tandem lung and bone marrow transplant [7]. Two authors (SEC and DH) recommend routine liver imaging such as FibroScan to evaluate for cryptogenic fibrosis or cirrhosis in all candidates with short telomeres. We do not, however, recommend routine liver biopsy as part of the transplant evaluation in the absence of imaging or biomarkers suggestive of hepatic dysfunction [6]. For potential candidates with hepatic fibrosis and elevated portal pressures or with cirrhosis, we recommend evaluation for combined lung-liver transplantation, when appropriate [8].



Hospital of the University of Pennsylvania Lung Transplant Program Guidelines:
Approach to Evaluation of Suspected Telomere Biology Disorder

Screening Algorithm:



^a Screening by Flow-FISH

^b Hepatology referral is warranted for individuals with liver imaging concerning for fibrosis or cirrhosis with or without evidence of portal hypertension

Figure 2. Sample algorithm for screening for short telomeres among patients with interstitial lung disease referred for lung transplant evaluation. Figure title adapted to reflect Telomere Biology Disorder terminology.

Transplant Outcomes

Although there is a growing literature on transplant outcomes among recipients with TBDs, differences in sample size, institutional management and immunosuppression protocols, and telomere length measurement assays make comparisons between reports difficult.

Several moderately-sized cohort studies have identified an association between short telomeres and increased post-transplant mortality and/or chronic lung allograft dysfunction (CLAD) [9-11]. For example, Newton et al found that recipients with ILD and telomeres below the 10th percentile had a 6-fold increased hazard for CLAD and a 10-fold increase hazard for death [10]. Swaminathan et al similarly reported higher mortality and CLAD among pulmonary fibrosis recipients with variants in *TERT*, *RTEL1*, and *PARN* [9]. More broadly, Courtwright et al found an association between decreased CLAD-free survival and shorter telomere length after transplant among all disease types, including cystic fibrosis and chronic obstructive pulmonary disease [12]. Importantly, however, despite the relative increase risk for mortality, overall survival for recipients with short telomeres in these studies has been in keeping with national benchmarks. In addition, not every study has shown an association between short telomeres and poor survival. For example, Faust et al did not find decreased CLAD-free mortality among short telomere recipients [13].

Even if the link between short telomeres and increased post-transplant mortality and/or CLAD is borne out in larger studies, the mechanisms behind this association remain unclear. It may be that recipients with short telomeres require immunosuppression reduction because of cytopenias, placing them at risk for CLAD. Alternatively, they may be more vulnerable to respiratory viral and other infections that are associated with CLAD, they may lack the replicative reserve to populate the donor organs with recipient-derived stem cells, or they may be more susceptible to fibroblast rather than epithelial proliferation following airway injury [14, 15].

Several other post-lung transplant outcomes aside from survival and chronic rejection have been reported in short telomere recipients. Popescu et al. identified impaired cytomegalovirus (CMV) immunity among patients with short telomeres and pulmonary fibrosis who underwent lung transplantation [16]. CMV reactivation was particularly common in mismatch recipients (CMV donor positive, recipient negative), which has been reported in other cohort studies in the short telomere lung transplant population [12]. There have also been case reports of bone marrow failure syndromes following

lung transplant, particularly for *TERT* variant carriers, as well as systemic graft-versus-host disease [5, 17]. Short telomere length, however, has not been associated with *de novo* donor specific antibody production or the development of more severe chronic kidney disease following transplant [11, 18]. There are also mixed associations between severe primary graft dysfunction and short telomeres [9, 10]. Some, but not all studies, have suggested decreased risk for acute cellular rejection—potentially related to impaired cellular immunity—among recipients with short telomeres [10, 11, 19].

Post-Transplant Management

While acknowledging the limitations of the current literature on post-transplant outcomes, we believe that there are steps that can be taken to optimize care pathways for lung transplant recipients with shortened telomeres. First, particularly for recipients with known hematologic manifestations, we recommend avoiding T cell depleting agents such as anti-thymocyte globulin (ATG), unless there is a strong clinical indication. ATG has been associated with increased telomere shortening and decreased telomerase activity in kidney transplant recipients and increases the risk of infectious complications following transplant [20]. Although a small case series did not show increased mortality among short telomere recipients with the use of the CD52 monoclonal antibody alemtuzumab, there was an increased incidence of neutropenia, thrombocytopenia, and need for red blood cell transfusion [21].

Second, given the apparent increased risk for CMV reactivation, we recommend lifelong CMV prophylaxis for recipients with TBDs, particularly among those who are CMV mismatches. Because valganciclovir, the most common CMV prophylaxis agent, is associated with bone marrow suppression, consideration should be given to alternative drugs such as letermovir. For CMV negative candidates, we do not recommend delaying lung transplant in favor of a CMV negative donor match given the potential for increased waitlist mortality. Finally, screening for post-lung transplant skin cancers is particularly

important in transplant recipients with TBDs, who are at high risk for these conditions (see also Chapter 6, Dermatologic Manifestations and Chapter 9, Solid Tumors) [22]. Correspondingly, the use of antifungal agents such as posaconazole or isavuconazonium should be considered, when indicated, rather than voriconazole given its association with skin cancer.

In the absence of clinical studies demonstrating post-lung transplant benefit, we do not recommend the routine use of danazol for lung transplant recipients with TBD-related mutations and refractory bone marrow suppression, including the pediatric population. Of particular concern is the potential for hepatic toxicity and venous thromboembolism in a population already at higher risk for these complications [23]. Similarly, although *in vitro* data have suggested that mammalian target of rapamycin (mTOR) may be associated with reduced telomere shortening compared to calcineurin inhibitors, we do not recommend routine use of mTOR inhibitors for TBD lung transplant recipients in the absence of another indication (e.g., chronic kidney disease, airway stenosis, etc.).

Conclusion

DC and the related TBDs are not a contraindication for lung transplantation, although early referral for lung transplant evaluations at an experienced center is warranted. Additional testing may be required to identify modifiable risks to tailor post-lung transplant management to achieve the best possible outcomes. When the evaluation identifies two-organ dysfunctions (lung-liver, lung-bone marrow), referral to specialized transplant centers for evaluation for dual transplantation is warranted.

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