Update in Lung Transplantation 2013

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Abstract

Research in pulmonary transplantation is actively evolving in quality and scope to meet the challenges of a growing population of lung allograft recipients. In 2013, research groups leveraged large publicly available datasets in addition to multicenter research networks and single-center studies to make significant

contributions to our knowledge and clinical care in the areas of donor use, clinical transplant outcomes, mechanisms of rejection, infectious complications, and chronic allograft dysfunction.

Keywords: lung transplantation; donor; rejection; infection; bronchiolitis obliterans syndrome

Current Status of Lung Transplantation

In contrast to other commonly transplanted solid organs, International Society for Heart and Lung Transplantation registry data indicate continued growth in lung transplant volumes (1). More than 3,600 adult lung transplantation procedures were reported in the most recently updated year, representing the highest number performed in a single year to date. The percentage of transplant operations performed for interstitial lung disease has increased rapidly over the last decade, now accounting for 29% of all transplants. Older patients represent an important growing subset of lung recipients internationally (1); however, given an aging population and changes in lung allocation priorities, this trend is even more striking in the United States, where 26% of candidates on the lung waiting list in 2012 were aged 65 years or older as compared with just 6% in 2004 (2).

Short-term survival after lung transplantation has improved in recent years as compared with earlier eras, with 3-month survival now at 90% and 1-year survival having improved to 81%. Long-term survival, however, remains relatively unchanged and is limited to a median of 5.6 years, principally due to the development of infection and/or chronic lung allograft failure (1). Importantly, both international and U.S.-based registry data suggest advanced age may negatively impact long-term post-transplant outcomes and predisposes to select complications, such as malignancy (1, 2).

Donor Use

The number of potential candidates who could benefit from lung transplantation far exceeds the number of lung transplant operations performed annually. This is particularly true in pediatrics, where in the past year existing allocation practices were

challenged and a pediatric patient successfully petitioned for listing as an adult, raising both medical and legal issues for the transplant community (3, 4). Currently less than 2% of all transplanted donor lungs are procured after circulatory death (5). Consequently, donation after circulatory determination of death (DCDD) may represent a promising strategy to increase donor use.

In response to the need for increased organ availability for all potential recipients, the American Thoracic Society Health Policy Committee released a joint statement with the International Society for Heart and Lung Transplantation, Society of Critical Care Medicine, United Network for Organ Sharing (UNOS), and the Association of Organ Procurement Organizations considering matters of ethics and policy related to controlled DCDD (6). The statement places emphasis on high-quality palliative care for dying patients, early Association of Organ Procurement

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Organizations notification, thorough conversations with surrogates regarding expectations, and effective collaboration among skilled personnel to derive a plan that will best support viable organ donation and alleviation of suffering (6).

Reported outcomes after transplantation of DCDD lungs have been generally positive in relatively small, single-center series (7–11). To further understand the clinical implications of donation after a period of cardiac arrest, Castleberry and colleagues (12) analyzed UNOS registry data to compare the outcomes of 479 lung recipients from brain-dead donors who had suffered cardiopulmonary arrest and subsequent resuscitation (arrest/resuscitation) to propensity-matched control subjects or all remaining non-arrest/resuscitation donor recipients to report that unadjusted median overall survival and common early postoperative complications are similar among these three groups. Importantly median PaO₂ on 100% inspired oxygen was comparable in arrest/resuscitation donors as compared with all other donor lungs (12).

In recent years there has been an observed trend toward increasing use of organs from older donors (1), presumably to meet growing demands. Leveraging data from the Organ Procurement and Transplantation Network, Baldwin and colleagues (13) assessed the impact of donor age, particularly older donor age, on lung recipient outcomes in the modern lung transplant era. The rate of 1-year graft failure was the lowest among donors aged 30 to 50 years and began to rise for donors older than age 50 years. The magnitude of the association between graft failure and donor age 50 to 64 years was small; however, this effect was of most notable impact when differing recipient characteristics were considered, such as higher lung allocation score (LAS) or need for mechanical ventilation bridge to transplant. In contrast, recipients of lungs from donors aged 65 years or older had a more than twofold increased rate of 1-year graft failure (hazard ratio, 2.15; 95% CI, 1.47–3.15) when accounting for relevant recipient, donor, and procedure characteristics (13).

Together these studies examining the impact of donor age and cardiac arrest/resuscitation status offer encouraging data that may support the safe expansion of the donor pool to include DCDD (providing the donor lung meets standard acceptability

metrics) and donors aged 55 to 64 years, particularly for recipients with lower LAS. Studies examining DCDD and ongoing exciting work to increase the number or quality of usable donor lungs, including innovations in *ex vivo* lung perfusion (14), will enable further growth in lung transplant volumes and diminish disparities between organ availability and the increasing burden of end-stage lung disease.

Survival and Quality of Life

Since 2005, adult lungs have been allocated in the United States according to the LAS (15). Although this practice has effectively reduced waitlist deaths, several groups have observed that transplant recipients with higher LAS scores also have higher post-transplant mortality (16–18) and therefore may not attain the expected net transplant benefit. During the patient's time on the lung waitlist, the LAS may be updated in response to clinical changes, or at least every 6 months.

Using UNOS registry data, Tsuang and colleagues (19) investigated the clinical implications of LAS dynamics in the 30 days before transplantation. Change in LAS (LAS Δ) was considered as a dichotomous or continuous covariate. Twelve percent of the studied cohort had an LAS Δ greater than 5 for 30 or more days preceding transplantation. Notably, these patients had consistently worse post-transplant survival rates when compared with those with a stable LAS or smaller LAS Δ , independent of the respective LAS value at transplantation. When LAS change was examined as a continuous covariate, similar results were observed with an increased hazard of post-transplantation death for LAS change values of 2.5 and above (19). This novel observation may be of particular interest to public policy makers as it suggests further revisions to the lung allocation algorithm should focus on the dynamics of the composite score in addition to the actual score itself in predicting post-transplant survival.

Establishing the net survival benefit conferred by lung transplantation remains an area of active interest, yet is particularly challenging to determine given lack of randomized clinical trials and fundamental limitations in UNOS data for this purpose. Previous research examining survival

benefit in patients with cystic fibrosis (CF) called into question the usefulness of transplant for this population (20). The generalizability of these results, however, is uncertain, given use of older-era transplant outcomes, inherent bias in statistical methodology, and inclusion of UNOS data before LAS implementation. Thabut and colleagues (21) therefore assessed net transplant benefit in adult patients with CF using UNOS data available after the implementation of the LAS. Additionally, this work used an innovative statistical approach to assimilate longitudinal data related to LAS trajectory while on the waitlist, thus improving modeling of patient outcomes (22). These analyses suggest that lung transplant conferred a survival benefit for patients with CF with LAS scores greater than 30 at the time of listing, which included all but one patient receiving a transplant within the studied period. Hence, using rigorous statistical approaches, there is convincing evidence for a survival benefit of lung transplant for nearly all adult patients with CF who have undergone pulmonary transplantation in the LAS era (21).

Although survival and other clinical end points continue to be the primary focus of most lung transplant research, relatively few studies have explored important patient-reported outcomes. Finlen Copeland and colleagues (23) assessed the impact of lung transplant on quality of life (QOL) using prospective, serially collected Medical Outcomes Study 36-Item Short-Form Health Survey data as a secondary analysis from a multicenter cytomegalovirus prevention trial (24). Notably, pretransplant baseline physical and mental QOL were far below normative population values. Over the course of post-transplant Year 1, physical QOL scores increased significantly from baseline and neared population norms. In contrast, scores reflecting perceived psychological well-being remained well below normative values. Thus, increased attention to support mood and psychological health is needed to maximize the potential QOL benefits of lung transplantation (23). Additionally, the development of novel patient-reported outcome tools in lung transplant recipients, as described by Singer and colleagues (25), may enhance our understanding of disability within this patient subset, enable assimilation of patient-centered metrics into transplant decision making, and help

address these unmet psychological needs in the future (26).

Primary Graft Dysfunction

Despite improving short-term lung transplant outcomes, primary graft dysfunction (PGD) remains an important clinical challenge, given its impact on survival and long-term allograft function (27, 28). Using data collected by the Lung Transplant Outcomes Group, a multicenter National Institutes of Health collaborative network, Diamond and associates (29) found an incidence of grade 3 PGD at 48 or 72 hours of 16.8%, with significant variation by center (range 2–27%), in an analysis of 1,255 lung recipients. Independent risk factors for grade 3 PGD included use of cardiopulmonary bypass, single-lung transplant, pulmonary hypertension, preoperative diagnosis of sarcoidosis, overweight or obese body mass index, large volume packed red blood cell transfusion, any history of donor smoking, and increased fraction of inspired oxygen at the time of allograft reperfusion. Furthermore, the development of grade 3 PGD was associated with a 23% absolute increase in the risk of death within 1 year of transplant. Importantly, several of these identified risk factors are modifiable and represent areas of attention, particularly with respect to intraoperative and perioperative recipient management or improved optimization practices for transplant candidates (29).

Beyond establishing clinical risk factors, additional studies published in 2013 provided insight into PGD phenotypes and mechanisms. Shah and colleagues (30), for example, used latent class modeling on Lung Transplant Outcomes Group subjects to determine that patients with persistent grade 3 PGD had higher mortality and were more likely to have had blood transfusion, pulmonary hypertension, or cardiopulmonary bypass use than those subjects who resolved PGD soon after transplant. These findings indicate there may be important pathophysiological differences that lead to sustained lung injury in this patient subset. In a complementary study examining gene expression in bronchoalveolar fluid (BALF) from lung allografts that develop PGD, Cantu and colleagues (31) demonstrated up-regulated transcript expression in innate

immune and inflammasome pathways, suggesting these pathways may play a key role in mediating early lung injury.

Mechanisms and Predictors of Rejection

Despite intensive immunosuppression, lung transplantation has the highest rate of acute and chronic rejection among all commonly transplanted solid organs. Thus, understanding the mechanisms and clinical predictors of lung rejection is necessary to develop new treatments and improve recipient outcomes.

As innate effector cells, such as neutrophils (32), have been demonstrated to play a key role in lung rejection, and it is now well understood that the initial innate immune response can shape subsequent adaptive immunity, Jungraithmayr and associates (33) investigated whether innate natural killer (NK) cells have an immunomodulatory role during experimental murine lung transplantation. Their findings indicate that NK cells mature, activate, and infiltrate the lung allograft early after lung transplantation. Furthermore, administration of IL-15/IL-15R α complexes induced expansion of NK cells within the allograft, decreased numbers and alloreactivity of infiltrating T cells, and thus attenuated allograft rejection. Further experiments indicated that the mechanism by which NK cells confer protection may be through removal of donor-derived dendritic cells from the allograft. These results provide an opportunity to consider whether preconditioning of lung recipients with regimens that augment NK cell reactivity may be beneficial for transplant outcomes (33).

Outside these early innate immune responses, a growing body of literature has implicated humoral immunity to human leukocyte antigens or self-antigens as important in mediating lung allograft rejection. In a study examining antibodies to the self-antigens K α 1 tubulin and collagen-V, Trivedi and colleagues (34) demonstrated that circulating self-antibodies in pretransplant sera were associated with a higher incidence of post-transplant BOS. Corresponding to these data on autoimmunity, both clinical and experimental evaluations indicate complement activation may be an important

stimulant in the cascade of events that leads to obliterative bronchiolitis (35), suggesting complement blockade may hold potential as a therapeutic strategy for BOS.

In addition to elucidating the mechanisms driving rejection responses, characterization of donor, recipient, and allograft-related factors that predict rejection remains an exciting and active area of research. Given prior studies demonstrating differential gene expression in endobronchial biopsy (EBBx) specimens procured from larger airways, Greenland and colleagues (36) hypothesized that large airway lymphocytic bronchitis detected by EBBx in the absence of infection identifies patients at risk for BOS. Their single-center analysis demonstrated that the maximum inflammation score derived from the EBBx at 90 days post transplant was more accurate than either traditional A- or B-grade rejection scores in predicting the development of BOS. This effect was primarily driven by a small proportion of the cohort with moderate to severe large airway inflammation (36). Although these findings require multicenter validation, EBBx represents a potential novel biomarker for BOS that could allow earlier therapeutic interventions in those at higher risk.

Beyond EBBx, additional innovative contributions this year suggest that measuring cytokine (37) or surfactant (38) expression in donor lungs even before implantation, genotyping recipients for polymorphisms in the IL-17A receptor gene (39), or measuring peripheral blood soluble receptor for advanced glycation end-product (sRAGE) levels immediately post transplant (40) may be valuable in identifying recipients at risk for rejection, BOS, or poor allograft survival. Ultimately, a combined risk assessment strategy that incorporates donor, recipient, and early allograft profiles may offer exciting potential to increasingly personalize post-transplant recipient management.

Infectious Complications

Three studies (41–43) published this year explored the complex relationship between the allograft microbiome and BOS and provided interesting insights related to two common post-transplant infectious complications, *Pseudomonas* and *Aspergillus*, for which prior studies offer

conflicting results regarding their influence on long-term lung transplant outcomes.

Given that proinflammatory CXC chemokines have been shown to associate with *Pseudomonas* infection and, furthermore, that *Pseudomonas* may influence the development of BOS, Gregson and colleagues (42) modeled the interaction between infection or colonization with *Pseudomonas*, concentrations of CXC chemokines in BALF, and movement from a stable post-transplant state to BOS or death. The researchers demonstrated a state-specific effect of *Pseudomonas* isolation after lung transplantation with infection (but not colonization) increasing the risk of moving into BOS or dying before BOS onset. Elevated levels of BALF CXC chemokines further increased the risk of developing BOS and dying after BOS onset. In particular, an interaction was observed with the concentration of allograft-derived CXCL1 and *Pseudomonas* infection in augmenting BOS risk. These novel findings implicate that the host inflammatory response and pathogen together influence clinical outcome (42).

In a related study, Willner and associates (43) cross-sectionally and longitudinally characterized microbial communities in lung allografts from recipients with and without BOS using high-throughput 16 sRNA gene amplicon pyrosequencing and demonstrated that reestablishment of recipient-associated microbiota in the lung allograft is associated with a reduced risk of BOS. In contrast, the acquisition of *de novo* microbial populations increased BOS risk. Interestingly, despite a significantly higher microbial biomass, patients receiving lung transplant consistently demonstrated less microbiota diversity as compared with control patients (43). Whether this restricted microbial diversity in and of itself has important immunologic consequences within the alloimmune environment is an exciting area of evolving research. Additionally, the authors observed no association between *Pseudomonas* and BOS when microbial concordance was considered. Although a smaller study and inherent potential for confounding due to antimicrobial therapy given a large proportion of recipients with CF, these results, together with those of Gregson and colleagues (42), suggest that *de novo* *pseudomonas* infection (as opposed to either colonization or recolonization) may

have an important impact on post-transplant outcomes.

Importantly, in both of these prior cohort studies the finding of *Aspergillus* on respiratory culture was significantly associated with BOS. Weigt and colleagues (41) expanded these findings by further assessing the significance of *Aspergillus* species depending on their reported conidial size, as this property determines the probability that colonization occurs within the small airways where the pathology of obliterative bronchiolitis occurs. Their findings from two large independent cohorts of lung recipients validate a significant increase in the risk for BOS and post-transplant death associated with infection with small conidia *Aspergillus* species (*fumigatus*, *nidulans*, *terreus*, *flavipes*). In contrast, *Aspergillus* species of large conidial size, such as *niger*, *flavus*, *ustus*, and *clavatus*, did not have an observed clinical impact. These disparate findings based on conidial size are of particular interest in that they suggest *Aspergillus* colonization may be involved in BOS pathogenesis and, thereby, merit further study to determine a causal role or evaluate antifungal prophylaxis strategies in preserving long-term graft function (41).

Chronic Lung Allograft Dysfunction

Chronic lung allograft dysfunction (CLAD) is increasingly used to describe a condition of sustained impairment in lung allograft function and represents the principal factor limiting long-term survival after lung transplantation. Although BOS has served as an important descriptor of allograft dysfunction and is the most commonly observed CLAD phenotype, it is increasingly recognized that some lung recipients develop progressive allograft dysfunction with clinical features atypical for BOS. Investigation into the phenotypes of CLAD remains an area of active research in lung transplantation. The term restrictive allograft syndrome (RAS) has been developed to describe a CLAD phenotype characterized by restrictive physiology, radiographic infiltrates, and histology consistent with diffuse alveolar damage (DAD), interstitial fibrosis (44), and, more recently, pleuroparenchymal fibroelastosis (45). Patients with RAS are observed to

follow a clinical course marked by one or more respiratory exacerbations, ultimately leading to respiratory failure and death (46).

Shino and colleagues (47) have further extended our understanding of RAS, demonstrating that although DAD was a relatively uncommon event—affecting only 12% of recipients (or 4% of studied biopsies)—an episode of DAD observed on transbronchial biopsy is strongly associated with an increased future risk of RAS and death. Moreover, the authors made the novel observation that ligands for CXCR3, which serve as potent mononuclear cell chemoattractants, are markedly elevated in the BALF during episodes of DAD and that prolonged elevations of these chemokines in serial BALF samples predicted the development of CLAD. These data suggest that allograft injury patterns are associated with aberrant Th1 immune responses and, furthermore, that CXCR3 may be exploited as a therapeutic target to attenuate lung inflammation or fibrosis (47).

Paraskeva and colleagues (48) applied a multimodal approach to CLAD classification, with the greatest weight placed on histopathology, to identify another subphenotype of clinical and prognostic significance. Using this approach, the authors concluded that a CLAD phenotype distinguished by the histologic finding of acute fibrinoid organizing pneumonia (AFOP) exists and that patients with this phenotype experience a poor prognosis and higher risk for death as compared with BOS. Patients with AFOP were more likely to have nonobstructive physiology and radiographic patterns inconsistent with BOS, such as ground-glass changes and interlobular septal thickening. Interestingly, the histology of AFOP is distinct from that of DAD and was not observed concurrent with DAD; hence, although it is clear that both RAS and AFOP are divergent from BOS, it remains uncertain to what extent AFOP and RAS overlap (48).

An approach to CLAD phenotyping that is based on standardized procedures routinely obtained at all lung transplant centers and prospectively applied at CLAD onset may prove more generalizable. An analysis that explored one such approach (49) among patients with CLAD described that those with a spirometric pattern characterized by loss of FVC at CLAD onset relative to baseline (termed restrictive

CLAD), experienced worse survival after the onset of CLAD as compared with those with preserved FVC as is typical of BOS. Furthermore, in a subset of patients with available radiographic and histologic data, those with FVC loss were more likely to have radiographic alveolar or interstitial infiltrates and histologic findings of interstitial fibrosis, whereas patients with preserved FVC had findings more consistent with BOS, for example air trapping and histologically active bronchiolitis (49).

Continued work in the area of CLAD classification will be necessary to refine these approaches (50) so as to improve phenotypic homogeneity and, furthermore, to discern distinguishing or overlapping risk factors, mechanisms, and therapeutic

interventions (51) for these newly described CLAD phenotypes.

Conclusions

Lung transplant recipients represent the fastest-growing segment of solid organ transplant recipients; however, the epidemiology of patients undergoing transplantation has changed significantly as compared with earlier eras, with a large increase in the proportion of older recipients and those with interstitial lung disease. Research published in 2013 offers significant insights that may lead to improvements in donor lung use, alteration of practice patterns to mitigate early postoperative complications, refinement of phenotypic

classification and biomarkers for CLAD, and identification of novel potential therapeutic targets to diminish allograft rejection. Additionally, these recently published studies hold important implications for public policy makers and lung allocation strategies. Despite this progress, long-term lung transplant outcomes remain disappointing. Continued advances in the field will require well-coordinated multicenter clinical research to refine and validate single-center observations and more effectively translate basic findings into novel therapeutics through rigorous clinical trials. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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