Lung Transplantation for Hypersensitivity Pneumonitis

Ryan M. Kern, MD; Jonathan P. Singer, MD, MPH; Laura Koth, MD; Joshua Mooney, MD; Jeff Golden, MD; Steven Hays, MD; John Greenland, MD, PhD; Paul Wolters, MD; Emily Ghio, MSc; Kirk D. Jones, MD; Lorriana Leard, MD, FCCP; Jasleen Kukreja, MD, MPH; and Paul D. Blanc, MD, MSPH, FCCP

BACKGROUND: Hypersensitivity pneumonitis (HP) is an inhaled antigen-mediated interstitial lung disease (ILD). Advanced disease may necessitate the need for lung transplantation. There are no published studies addressing lung transplant outcomes in HP. We characterized HP outcomes compared with referents undergoing lung transplantation for idiopathic pulmonary fibrosis (IPF).

METHODS: To identify HP cases, we reviewed records for all ILD lung transplantation cases at our institution from 2000 to 2013. We compared clinical characteristics, survival, and acute and chronic rejection for lung transplant recipients with HP to referents with IPF. We also reviewed diagnoses of HP discovered only by explant pathology and looked for evidence of recurrent HP after transplant. Survival was compared using Kaplan-Meier methods and Cox proportional hazard modeling.

RESULTS: We analyzed 31 subjects with HP and 91 with IPF among 183 cases undergoing lung transplantation for ILD. Survival at 1, 3, and 5 years after lung transplant in HP compared with IPF was 96%, 89%, and 89% vs 86%, 67%, and 49%, respectively. Subjects with HP manifested a reduced adjusted risk for death compared with subjects with IPF (hazard ratio, 0.25; 95% CI, 0.08-0.74; $P = .013$). Of the 31 cases, the diagnosis of HP was unexpectedly made at explant in five (16%). Two subjects developed recurrent HP in their allografts.

CONCLUSIONS: Overall, subjects with HP have excellent medium-term survival after lung transplantation and, relative to IPF, a reduced risk for death. HP may be initially discovered only by review of the explant pathology. Notably, HP may recur in the allograft.

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ABBREVIATIONS: BOS = bronchiolitis obliterans syndrome; fBOS = freedom from bronchiolitis obliterans syndrome; HP = hypersensitivity pneumonitis; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; LT = lung transplantation; TBbx = transbronchial biopsy specimen; UNOS = United Network for Organ Sharing

AFFILIATIONS: From the Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine (Drs Kern, Singer, Koth, Golden, Hays, Greenland, Wolters, Leard, and Blanc and Ms Ghio), Department of Pathology, Pulmonary Pathology and Cytopathology (Dr Jones), Division of Cardiothoracic Surgery (Dr Kukreja), and Division of Occupational and Environmental Medicine (Dr Blanc), University of California San Francisco, San Francisco; and the Division of Pulmonary and Critical Care Medicine (Dr Mooney), Stanford University, Palo Alto, CA.

Dr Kern is currently at the Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic (Rochester, MN).

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CORRESPONDENCE TO: Ryan Kern, MD, 200 First St SW, Rochester, MN 55905; e-mail: ryanmkern@gmail.com

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Hypersensitivity pneumonitis (HP) is a rare and complex interstitial lung disease (ILD) triggered by inhaled antigens, with multiple known causative agents.¹⁻⁹ Treatment is primarily aimed at identifying and avoiding the implicated antigen.^{1,10,11} Identifying the offending antigen, however, is achieved only in about 40% of cases.^{1,12} Further, a subset of patients develop progressive fibrosis and have a high mortality risk.¹³ Lung transplantation (LT) may be considered in such cases.

Although the median survival after LT is approximately 5 years, there is significant heterogeneity in outcomes depending on the indication for this intervention.¹⁴ Critically, no studies have reported survival after LT for HP, thus precluding counseling on postoperative mor-

tality risk specific to this condition. Moreover, because HP is triggered by environmental factors, ongoing antigenic stimulation theoretically could drive disease recurrence or accelerate graft failure despite immunosuppressive therapy, raising further questions about diagnosis-specific survival. To address these knowledge gaps, we assessed key clinical outcomes following LT for HP in comparison with patients who underwent transplantation for idiopathic pulmonary fibrosis (IPF). We hypothesized that there would be no difference in survival after LT for HP compared with IPF. We also assessed other clinically important outcome measures, including diagnosis of HP following LT based on explant pathology and recurrent HP in the allograft, a phenomenon not previously reported.

Materials and Methods

Study Population and Subject Identification

We performed a retrospective cohort study of all patients undergoing LT for HP between January 1, 2000, and July 1, 2013, at the University of California San Francisco. Follow-up continued through December 31, 2013. Subjects undergoing LT for IPF during the same time period were selected as referents. The analysis was approved as part of an institutionally reviewed protocol for LT outcomes assessment at our center (institutional review board number 13-10676). Some of these data have been presented in abstract form.¹⁵⁻¹⁷

Potential subjects were identified by review of listing diagnoses submitted to the United Network for Organ Sharing (UNOS). We identified subjects transplanted for the following UNOS listing diagnosis codes: HP (code 420), granulomatous lung disease (109); occupational lung disease (1610); IPF (1604); usual interstitial pneumonia (453); pulmonary fibrosis other (1613); "other" (1999). Importantly for this study, UNOS diagnoses do not necessarily reflect the ultimate clinical consensus before LT nor are they typically revised if review of the lung explant pathology after LT identifies a disease other than that listed. We assessed misclassification in light of these factors. With experts in ILD, chest radiology, and chest pathology, we re-reviewed available pretransplant clinical notes, radiology images, and video-assisted thoracoscopic surgical biopsy specimens. When the pre-LT data reflected a consensus diagnosis of HP made by our University of California San Francisco ILD multidisciplinary committee¹⁸ using established criteria for diagnosing HP,¹² we assigned that diagnosis (Fig 1). When the explant pathology was suggestive of HP but a pre-LT consensus of HP had not been determined, the case was represented to the group. Based on this approach, 31 HP cases ultimately were identified. We used the American Thoracic Society/European Respiratory Society guidelines¹⁹ to identify referents with IPF (n = 91) from among the patients who underwent LT.

Posttransplantation Care

As reported previously,²⁰ all patients at the University of California San Francisco facility are maintained on an immunosuppression regimen of prednisone, tacrolimus, and mycophenolate mofetil and undergo allograft surveillance (spirometry, chest CT scan, and bronchoscopy with transbronchial biopsy) to evaluate acute rejection eight times in the first 24 postoperative months (e-Appendix 1).

Clinical Measurements

Pre-LT variables, including demographics, antigen exposure, smoking history, BMI, spirometry, mean pulmonary artery pressure, lung allocation score, use of chronic oral steroids, and date and type of LT (single

vs bilateral), were abstracted through chart review and the UNOS registry. Antigen exposures were classified into avian, microbial, or unknown (no suspect antigen identified). Abstracted donor factors included age and ischemic time. We defined recurrent HP as the presence of all of the following: spirometric evidence of obstruction, likely antigen exposure, CT scan evidence of new ground-glass changes or air trapping, and poorly formed granulomas, seen in transbronchial biopsy specimen, not explained by infection.

Outcomes

Our primary study outcome was time to death or retransplant. Vital status was obtained by review of the Social Security Master Death Index and chart analysis. Secondary outcomes included rate of acute rejection and freedom from bronchiolitis obliterans syndrome (fBOS). Acute cellular rejection was defined as $\geq$ A2 requiring treatment in the first year²¹; fBOS, as less than stage 1.²²

Statistical Analysis

Baseline characteristics were compared by χ^2 test or Wilcoxon rank-sum test. Survival and fBOS were estimated using Kaplan-Meier methods. Equality of survivor functions was tested by log-rank test. Multivariate

Figure 1 – Identification of subjects with HP and IPF. Group “D” = UNOS listing group diagnosis code for restrictive lung disease; HP = hypersensitivity pneumonitis; IPF = idiopathic pulmonary fibrosis; LT = lung transplant; UNOS = United Network for Organ Sharing.

Cox proportional hazard regression was used to test the relative hazard of death, adjusting for sex, type of LT (single vs bilateral), BMI, creatinine level, age, and acute rejection requiring treatment in the first year after LT. Incidence of acute rejection was compared using χ^2 . We

also compared the UNOS listing diagnoses of HP against our ultimate diagnostic determination, calculating the UNOS diagnostic sensitivity and related 95% CIs. Analyses were performed using Stata 12.1 (StataCorp LP).

Results

Subject Characteristics

Of 406 LTs performed, 31 were for HP (7.6%). Compared with subjects with IPF, those with HP were more frequently women (48% vs 28%, $P = .03$), had lower FVC % predicted (38% vs 50%, $P < .001$), and were more likely to be taking corticosteroids at time of LT (77% vs 49%, $P = .007$) (Table 1). There were no statistically significant differences in age, race/ethnicity, ever smokers, BMI, creatinine level, mean pulmonary artery pressure, lung allocation score, donor age, ischemic time, or single vs double LT between groups (all $P > .10$). In the HP cohort, an inciting exposure was identified in 12 of 31 patients (39%). Of those, eight had exposure to birds, three to mold, and one to wood bark, possibly sequoia (redwood), a known cause of HP.²³

HP Diagnoses

Of 31 cases diagnosed with HP before transplantation, there were four for whom the UNOS-listed diagnosis did not conform to the clinical consensus reflected in the medical record. The diagnosis of HP was made after LT in another five subjects (16%) only after review of lung explant pathology. In each of these five cases, the presumed diagnosis before LT was IPF. In three other cases, the diagnosis was not confirmed before transplantation, although HP was listed in the differential diagnosis in clinical notes. An identifiable exposure to mold was suspected in one subject only after LT and another subject was believed to have had exposure to birds in the form of down feathers. Thus, of 31 cases, only 19 had a UNOS listing diagnosis of HP (sensitivity, 61%; 95% CI, 42%-78%). Of the 26 subjects with a diagnosis of HP

TABLE 1 Baseline Characteristics for 122 Subjects Undergoing Lung Transplant for HP or IPF

Baseline Characteristic	HP (n = 31)	IPF (n = 91)	P Value
Age, y	56.9 ± 9.4	59.7 ± 7.7	.19
Male sex	16 (51.6)	66 (72.5)	.032 ^a
Race			.50
White, non-Hispanic	24 (77.4)	70 (76.9)	
Hispanic	5 (16.1)	9 (9.9)	
Other	2 (6.5)	12 (2.2)	
Exposure			...
Avian	8 (25.8)	n/a	
Microbial	4 (12.9)	n/a	
Unknown	19 (61.3)	n/a	
Ever smoker	16 (51.6)	52 (57.1)	.59
BMI	25.6 ± 4.1	26.1 ± 3.9	.50
Creatinine level	0.83 ± 0.23	0.90 ± 0.26	.20
FEV ₁ % predicted	42.1 ± 14.1	54.4 ± 16.8	< .001 ^a
FVC % predicted	37.6 ± 12.5	49.9 ± 16.1	< .001 ^a
FEV ₁ /FVC	0.85	0.84	.44
Mean PAP, mm Hg	23.0 ± 8.9	22.8 ± 9.6	.92
Lung allocation score	56.3 ± 14.9	56.5 ± 19.4	.42
Chronic oral steroids before transplant	24 (77.4)	43 (49.4)	< .05 ^a
Donor age, y	33.4 ± 14.6	32.7 ± 13.4	.81
Bilateral lung transplant	27 (87.1)	68 (74.7)	.15
Ischemic time, h	5.47 ± 0.96	5.50 ± 1.41	.91

Data presented as mean ± SD or No. (%). HP = hypersensitivity pneumonitis; IPF = idiopathic pulmonary fibrosis; PAP = pulmonary artery pressure.

^aStatistically significant at $P \leq .05$.

pretransplant, explant pathology revealed classic pathologic findings of HP in 22 (85%), a nonspecific interstitial pneumonia pattern in two (8%), and usual interstitial pneumonia with some features suggestive of HP in two (8%).

Recurrent HP

HP recurred in two of 31 subjects (6%). A third subject was deemed to have possible recurrent HP based on poorly formed granulomas identified on transbronchial biopsy specimen (TBBx) with no infectious source. Since we were not able to confirm reexposure to a suspect antigen, this case did not meet our strict criteria for recurrence (see Materials and Methods section).

The first subject underwent single, right-sided LT in January 2006 at age 60 years following heavy occupational exposure to trees, possibly sequoias.²³ After LT, he returned to live in a heavily wooded area. Six months post-LT, his FEV₁ fell from 2.96 L to 2.63 L, and chest CT scan demonstrated new air trapping. BAL was negative for infection or lymphocytosis; TBBx demonstrated poorly formed granulomas and no rejection. After a 4-week absence from his residence and brief augmentation of prednisone, the patient's FEV₁ returned to baseline. A month after returning to the same residence, his FEV₁ fell again; repeated TBBx at 7 and 9 months post-LT again showed poorly formed granulomas. To avoid antigen exposure, the patient moved to a desert climate with resultant resolution of granulomas on all subsequent TBBx assessments. He is currently free from bronchiolitis obliterans syndrome (BOS) 7 years after LT.

The second subject underwent bilateral LT in March 2009 at age 49 years, following heavy exposure to mold and birds. HP serologies were positive for both fungal and avian precipitins. During the third post-LT year, the patient developed progressive dyspnea and declining FEV₁, with a CT scan that demonstrated air trapping. Bronchoscopies with BAL and TBBx performed twice over 1 month demonstrated a lymphocytosis (24% and 29%, respectively; CD4:CD8, 0.7), poorly formed granulomas, and negative microbiology. The subject reported new exposure to pigeons roosting outside her window. Prednisone was augmented for 1 month, then tapered. Spirometry stabilized but did not improve. Although subsequent TBBx assessments have shown no recurrence of the granulomas, she has been unable to relocate for financial reasons. At 5 years post-LT, the patient has grade 3 BOS, possibly related to recurrent HP.

The third subject with possible recurrent HP, but not meeting our study definition, had chronic exposure to

down feathers pre-LT. The post-LT course has been complicated with a declining FEV₁ that is likely multifactorial in etiology. Eight months post-LT, a single poorly formed granuloma was noted on TBBx, but the CT scan did not reveal air trapping or other features consistent with HP.

Survival

Survival after LT was significantly better in the HP group compared with the IPF group ($P = .005$): at 1, 3, and 5 years, 96%, 89%, and 89% for HP, respectively, vs 86%, 67%, and 49%, for IPF, respectively (Fig 2). The median follow-up times for survivors in the HP and IPF cohorts were 3.6 years (25%, 1.7 years; 75%, 6.8 years) and 3.3 years (25%, 2.3 years; 75%, 5.8 years), respectively ($P = .89$). After adjustment for covariates, those with HP experienced a fourfold relative-risk reduction for death compared with IPF (hazard ratio, 0.25; 95% CI, 0.08-0.74; $P = .013$) (Table 2).

Acute Rejection and BOS

Acute rejection requiring treatment in the first year was less common for HP than IPF (10% vs 31%, $P = .03$). There was, however, no statistically significant difference in fBOS between the HP and IPF groups ($P = .17$) (Fig 3). The 1-, 3-, and 5-year rates of fBOS were 89%, 84%, and 84%, respectively, for HP compared with 86%, 66%, and 55%, respectively, for IPF.

Discussion

The diagnosis of HP is difficult and, even when pathologically confirmed (sometimes only after transplantation), the initiating insult often remains obscure. We newly identified HP as one of a select group of respiratory

Figure 2 – Survival after lung transplantation for HP compared with IPF. Kaplan-Meier plot stratifying patients who underwent lung transplant for HP or IPF. The outcome was death or retransplant during the study period. See Figure 1 legend for expansion of abbreviations.

TABLE 2] Univariate and Multivariate Survival Analysis after LT comparing HP to IPF

Variable	HR	95% CI	P Value
Univariate analyses			
Diagnosis of HP	0.25	0.09-0.71	.009 ^a
Male sex	1.28	0.64-2.54	.488
Bilateral LT	0.33	0.18-0.61	<.001 ^a
BMI, per 5 units	1.63	1.10-2.42	.016 ^a
Age, per 5 y	1.29	1.05-1.58	.016 ^a
Creatinine, per 0.1 mg/dL	1.20	1.07-1.34	.002 ^a
Ever smoker	1.21	0.66-2.24	.534
Acute rejection (at least one treated episode in first year after LT)	1.49	0.80-2.80	.209
Multivariate analyses^b			
Diagnosis HP	0.25	0.08-0.74	.013 ^a
Bilateral LT	0.32	0.16-0.64	.001 ^a
BMI, per 5 units	1.79	1.17-2.73	.080
Age, per 5 y	1.17	0.95-1.45	.151
Creatinine level, per 0.1 mg/dL	1.13	1.00-1.28	.059
Acute rejection	0.73	0.35-1.49	.385

HR = hazard ratio. See Table 1 legend for expansion of other abbreviations.

^aStatistically significant at $P \leq .05$.

^bThe multivariate analysis includes all of the variables listed under that subheading.

conditions that may recur in the allograft after LT. Yet, in this single-center cohort study, we found that survival following LT for HP is excellent and surpasses that of patients with IPF. Although patients with HP have an

exaggerated immune response to inhaled antigens, compared with IPF (the prototypical ILD undergoing LT), HP cases manifested lower rates of acute rejection and lower, albeit not statistically significant, rates of BOS.

The survival advantage favoring HP compared with IPF we observed raises the possibility that the very immunologic abnormalities that underpin the HP disease process may provide an advantage in post-LT graft success. In that light, it is noteworthy that the rate of acute rejection in HP was approximately 10%. International averages for acute rejection requiring treatment in the first year for all subjects undergoing LT is 30% (similar to the rate in our IPF group).¹⁴ While not statistically significant, subjects with HP were slightly younger and slightly more likely to undergo bilateral (compared with single) lung transplantation, both factors associated with improved survival after lung transplant.²⁴ Despite controlling for these factors in our multivariate survival model, it is possible that some of the survival benefit in the HP cohort may be attributable to differences in age and transplant type or other unmeasured confounders.

Recurrent primary disease after LT in the allograft can occur in sarcoidosis, lymphangioleiomyomatosis, pulmonary alveolar proteinosis, pulmonary Langerhans cell histiocytosis, diffuse panbronchiolitis, desquamative interstitial pneumonia, giant cell interstitial pneumonia, and α_1 antitrypsin-related emphysema.²⁵⁻³⁵ HP can now be added to that list.

In patients transplanted for sarcoidosis, the discovery of granulomas on transbronchial biopsy specimens may be clinically insignificant.^{36,37} In contrast, the detection of granulomas on transbronchial lung biopsy specimens from patients after LT for HP should trigger clinical concern with urgent review of potential antigen exposures and consideration of changes to the patient's environment, immunosuppression regimen, and allograft monitoring schedule. Polymorphisms associated with major histocompatibility class 2 molecules, including human leukocyte antigen-DR and DQ, have been associated with increased risk for HP,^{38,39} suggestive of a role for adaptive responses. Recurrence of HP may be associated with persistent autoimmunity, de novo immune responses, or other nonimmune factors.

In HP, preventing and treating recurrent disease is challenging if the exposure cannot be identified and avoided. In our two cases of recurrent disease, there was pathologic resolution of granulomas and improvement or stabilization in spirometry after treatment-augmented

Figure 3 – Freedom from BOS for HP compared with IPF. Kaplan-Meier plot stratifying patients who underwent lung transplantation for HP or IPF. The outcome was freedom from BOS. The total number at risk excludes nonsurvivors. BOS = bronchiolitis obliterans syndrome. See Figure 1 legend for expansion of other abbreviations.

corticosteroids. Nonetheless, one subject moved to a new state and has remained BOS free, while the subject who was unable to relocate now has advanced BOS possibly related to recurrent HP.

In five subjects, the initial diagnosis of HP was made only after explant pathology review. On pathology, HP classically is associated with poorly formed granulomas, peribronchiolar fibrosis, and interstitial pneumonitis.⁴⁰ For our study, in the absence of an exposure, we required explant pathology to demonstrate these features to assign the diagnosis if HP had not been diagnosed by our multidisciplinary ILD committee prior to LT. On pathology, however, HP can manifest in usual interstitial pneumonia or nonspecific interstitial pneumonia patterns, as well as a pattern of mixed features.⁴⁰⁻⁴² Therefore, it is likely that even with our additional explant review, we underestimated the true prevalence of HP. One series evaluating pathologic diagnosis of native lungs in 175 LT recipients found two unexpected cases of HP.⁴³ Another study of 46 subjects diagnosed with IPF based on American Thoracic Society criteria¹⁹ found that 20 (43%) had chronic HP by rereview of exposure history, video-assisted thoracoscopic surgical biopsy specimens, and explant pathology.⁴⁴ Along with these studies, our findings highlight the challenges of diagnosing advanced chronic HP and highlight the utility of performing review of explant pathology after LT for fibrotic ILD.

Although there are inherent limitations to a single-center series of patients who have undergone LT, we had access to all available recipient-level data to maximize accurate diagnoses of HP or IPF. Further, we were able to longitudinally follow individual subjects and their potential exposures, affording us the opportunity to diagnose recurrent HP. Registry data can be immensely valuable with respect to sample size and multicenter data; however, this source is also vulnerable to diagnostic misclassification. In the case of LT, listing diagnoses may not reflect the ultimate pre-LT clinical consensus nor are they typically changed in light of explant pathology review. According to registry data, there were 125 cases of LT for HP in the United States during our study period.⁴⁵ Based on our findings, this may be a considerable underestimation.

Our study limitations should temper interpretation of its findings. Due to the wide variety of provoking antigens associated with HP, the etiology varies regionally. Given that this was single-center study, it is possible that outcomes at other centers might differ. Approximately 8% of transplants at our center were for HP, compared with < 1% nationally during the same time period (and even an upward adjustment to double that prevalence would still be considerably lower than that we found).⁴⁵ Even with our higher prevalence, 31 cases still limit our ability to extensively investigate potential cofactors beyond demographic characteristics, although they do not explain the differences that we did observe. Although lung allocation scores did not differ substantively by HP status in this analysis, we are not in a position to systematically address the inter-relationship between lung allocation scoring and varying diagnoses among subsets of ILD. Another potential study limitation is a reduction over time at our institution in protocol-driven transbronchial biopsies posttransplant that might uncover asymptomatic granulomatous responses that could reflect recurrent HP, although clinically relevant lung function decline would trigger diagnostic evaluation. In particular, greater study number and longer follow-up could help clarify the potential role of BOS in HP-related survival differences. Identifying HP in the setting of advanced fibrosis can be very challenging, but our results indicate that it is important to establish a diagnosis of HP for prognostic and, potentially therapeutic, purposes for both before and after lung transplantation.

Conclusions

Lung transplantation is an important option for select candidates with advanced, chronic HP, but accurately identifying such candidates is by no means straightforward. Importantly, HP may recur in the allograft and negatively impact clinical outcomes. Thus, vigilance for ongoing antigen exposure and disease recurrence after LT for HP is important. The overall survival following LT in this group is good and appears to be improved compared with IPF, the most common ILD indication for LT. Moreover, less frequent acute cellular rejection in the first year after LT for HP and potentially reduced rates of BOS should be studied for any clues these phenomena may yield in terms of survival advantage.

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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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