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# A Prospective Observational Study of Hypogammaglobulinemia in the First Year After Lung Transplantation

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**Background.** Immunosuppressive therapies have led to improved survival for lung transplant (LT) recipients but these therapies can lead to hypogammaglobulinemia (HGG) and potentially an increased risk of infection. Large prospective studies have not been performed to evaluate the impact of HGG on outcomes for LT recipients. **Methods.** This is a single-center prospective observational study of LT recipients. Pretransplant and posttransplant IgG levels were measured and related to infection, rejection, antibiotic use, and immunosuppression use. **Results.** One hundred thirty-three LT recipients were prospectively evaluated. Pretransplant IgG values were higher than IgG values at the time of transplant or any time thereafter (all  $P < 0.0001$ ). Severe HGG (IgG  $< 400$  mg/dL) was highest at the time of transplant (32.4%) while at 3, 6, 9, and 12 months posttransplant the prevalence of severe HGG was 7.4%, 7.5%, 8.9%, and 6.3%, respectively. Severe HGG was associated with 2 or more pneumonias ( $P = 0.0006$ ) and increased number of antibiotic courses ( $P = 0.003$ ) compared with the subjects without severe HGG. Pretransplant IgG level and less than 30% of pretransplant protective pneumococcal antibody levels were identified as pretransplant risk factors for severe HGG. In multivariate analysis, chronic obstructive pulmonary disease as the underlying disease and the use of basiliximab as the induction agent in conjunction with higher prednisone and mycophenolate dosing were most predictive of severe HGG ( $P = 0.005$ ), whereas the combination of age, severe HGG and number of acute steroid courses were most predictive of total days of pneumonia ( $P = 0.0001$ ). **Conclusions.** Our large prospective study identifies risk factors for severe HGG after LT and demonstrates that LT recipients with severe HGG are at increased risk for recurrent pneumonias and more antibiotic courses.

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**H**ypogammaglobulinemia (HGG) is an immunodeficiency condition defined by decreased immunoglobulin (IG) concentration and antibody production that can be further

classified as primary or secondary.<sup>1</sup> Primary HGG is caused by a primary immune defect and IG replacement therapy (IGRT) is indicated for all primary HGG conditions with significantly impaired antibody production.<sup>2</sup> Secondary HGG has been associated with hematologic malignancies, protein loss, increased metabolic catabolism, malnourishment, and

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iatrogenic immunosuppression.<sup>3</sup> Therapeutic options in secondary HGG have not been clearly delineated because of the heterogeneity of underlying diseases and insufficient number of quality studies.

Lung transplantation is a lifesaving procedure in patients with end stage respiratory disease. The median survival of lung transplant (LT) recipients is 5.7 years, and the LT recipients who survive to 1 year after primary transplantation have a conditional median survival of 7.9 years. Infection is the most common early cause of death and accounts for 37.4 % of all known causes of death in the first year after LT.<sup>4</sup> Secondary HGG, defined as IgG level less than 700 mg/dL, is a common complication of LT seen in 63 % of all LT recipients in 1 meta-analysis of retrospective studies.<sup>5</sup> Severe HGG, defined as IgG less than 400 mg/dL, is present in 15 % of LT recipients and has been associated with an increased risk of cytomegalovirus (CMV) infection, fungal and respiratory infections, and 1-year all-cause mortality.<sup>5</sup>

We present the results of the first large prospective observational study of HGG in the first year after lung transplantation. In this study, we obtained serial IgG levels before and after LT and analyzed patient characteristics, occurrence of pneumonias, CMV infection, antibiotic use, rejection, and survival after LT in relation to the IgG level. We hypothesized that severe HGG would be associated with an increased burden of pneumonias and worse survival.

## PATIENTS AND METHODS

We performed a prospective observational study of 133 patients who underwent LT at our transplant center between February 2011 and June 2013. We enrolled 229 subjects in the study at the time of initial LT evaluation or immediately before LT in those patients who presented with acute organ failure. The exclusion criteria were patients younger than 18 years, anaphylaxis to IGRT, or already on IGRT. The subjects who did not undergo LT within a year of consent or who were removed from the LT list were withdrawn from the study. This study was approved by the University Institutional Review Board (PRO09090483).

IgG levels were obtained within a year before transplantation; at the time of transplantation (within 72 hours posttransplantation), and at 3, 6, 9, and 12 months posttransplantation. Hypogammaglobulinemia was defined as mild (IgG = 400-700 mg/dL) and severe (IgG level < 400 mg/dL). Pneumococcal antibody testing (13 pneumococcal strains) was obtained at the same time when pretransplant IgG levels were obtained. The pneumococcal antibody levels were interpreted as protective if equal or greater than 1.3 µg/mL. Moderate deficiency was defined as failure to have more than 70 % protective pneumococcal antibody levels and severe deficiency as failure to have more than 2 protective pneumococcal antibody levels. In addition, pretransplant pneumococcal vaccination (Pneumovax and Prevnar) occurred at variable times and at least 4 weeks before collection of pneumococcal antibody levels. All information related to occurrence, cause, and treatment of pneumonia; allograft function; and rejection was collected at these time points. Pneumonia was defined by the presence of both clinical and radiographic criteria: fever (temperature,  $\geq 38^{\circ}\text{C}$ ), cough, dyspnea, purulent expectoration, and/or changes in the previous characteristics of respiratory secretions; and chest X-ray or computed tomography

scan revealing a new or progressive alveolar or interstitial infiltrate or cavitation that could not be explained by any other noninfectious cause. Cytomegalovirus infection was defined by the detection of CMV DNA using our in-house assay. Antibiotic courses were defined as intravenous and oral antibiotics prescribed to the patient for any infection during the first-year posttransplant.

All patients received induction immunosuppression with alemtuzumab or basiliximab. Basiliximab was used in those patients who were primary CMV or Epstein-Barr virus mismatch and in patients with a previous history of malignancy. All patients were prescribed maintenance immunosuppression with a triple-drug regimen consisting of either a calcineurin inhibitor (tacrolimus or cyclosporine) together with a cell cycle inhibitor (mycophenolate mofetil [MMF] or azathioprine) and prednisone. The baseline prednisone dose used was 5 mg daily. Patients who had basiliximab induction received a higher dose of prednisone and were tapered to 5 mg daily. Immunosuppression medication doses and levels (if applicable) were collected at 3, 6, 9, and 12 months posttransplant. Pretransplant prednisone and other immunosuppressant dosing was collected at the time of initial transplant visit. All patients received fungal and CMV antibiotic prophylaxis and were maintained on indefinite *Pneumocystis jiroveci* prophylaxis.

The diagnosis and grading of acute cellular rejection (ACR) were carried out on the basis of the results of transbronchial biopsies and in accordance with the International Society for Heart and Lung Transplantation classification.<sup>6</sup> Lung biopsies were performed if clinically indicated or every 2 to 3 months during the first posttransplant year according to the surveillance bronchoscopy protocol in our program. The decision to treat patients with histologic evidence of ACR was dependent upon the clinical setting and the severity of the rejection. All patients who had ACR  $\geq$  A2 were treated after excluding lung infection. Minimal ACR (A1) was only treated in symptomatic patients and if associated with significant decline in their pulmonary function test values. The usual treatment of ACR included intravenous methylprednisolone (15 mg/kg, or 0.5-1 g intravenous daily) for 3 days. The follow-up bronchoscopy was performed 3 to 4 weeks after treatment of an ACR episode. If biopsy-proven ACR persisted after 2 courses of glucocorticoids, an alternate immunosuppressive agent, such as antithymocyte globulin (RATG) or alemtuzumab, was administered. The maintenance immunosuppression regimen was adjusted in patients with recurrent ACR or persistent evidence of biopsy-proven ACR by substituting tacrolimus for cyclosporine or mycophenolate for azathioprine or adding a mammalian target of rapamycin inhibitor.

Additional clinical information was collected on all patients including the number of intensive care unit (ICU), hospitalization and ventilation days after LT surgery, and if patients required cardiopulmonary bypass (CPB) and/or extracorporeal membrane oxygenation (ECMO) during LT surgery.

## Statistical Analysis

Data were analyzed by using the JMP software program (JMP Statistical discovery, Cary, NC). The  $\chi^2$  analysis was used for categorical variables. The continuous data were analyzed with Kruskal-Wallis testing or with Student *t* test, as appropriate. The results were reported as ratios and percentages of the entire cohort. A *P* value less than 0.05 was considered statistically significant. Simple regression was initially

used to evaluate the relationship between variables and the presence of severe HGG and days with pneumonias, respectively. Those variables with  $P$  values less than 0.1 were then subjected to multiple regression analysis. Those variables that were found to be independent predictors for the outcome ( $P < 0.05$ ) were selected for the final model, and a stepwise backward elimination process used the likelihood ratio test to eliminate variables that did not significantly contribute to the model.

## RESULTS

### Patient Characteristics

One hundred thirty-three patients underwent single ( $n = 8$ ) or double ( $n = 125$ ) LT and were included in the study. The patient characteristics are shown in Table 1. Eighty-two subjects (61.7%) were male and 123 (92.5%) were white. The median age at the time of transplant was 51 years (interquartile range [IQR], 50.5–66 years). Forty-six subjects were transplanted for idiopathic pulmonary fibrosis (34.6%), 40 had chronic obstructive pulmonary disease (COPD) (30.1%), 13 (9.8%) had cystic fibrosis, 12 (9.0%) had scleroderma, and 22 (16.5%) had other various pulmonary conditions (sarcoidosis, pulmonary hypertension, alpha-1 antitrypsin deficiency, and others). Alemtuzumab was used as the induction agent in 89 (66.9%) subjects, whereas the remainder received basiliximab. Cytomegalovirus viremia was found in 51.1% of patients at some point during the first year after transplant. The pathogens causing pneumonia are listed in Table 2. The pretransplant pneumococcal vaccination with Pneumovax and Prevnar 13 was confirmed in 83% and 17% of the patients, respectively.

### IgG Levels

Pretransplant, time of transplant, 3-month interval IgG values over the first year are shown in Figure 1 and Table 3. Pretransplant IgG values were higher than IgG values at the time of transplant or any time thereafter (all  $P < 0.0001$ ). IgG values at all posttransplant time points were significantly higher than IgG values at the time of transplant (Figure 1,  $P < 0.01$  for all intergroup comparisons). At the time of transplant, 32.4% of subjects had severe HGG, whereas at

**TABLE 1.**

#### Baseline subject demographic characteristics

Demographics	Underwent LT (n = 133)
Age: median (IQR), y	51 (50.5–66)
Sex, male/female, n, (%)	82 (61.7%)/51 (38.3%)
Race, white/AA/other, n (%)	123 (92.5%)/8 (6%)/2 (1.5%)
Diagnosis, n (%)	
IPF	46 (34.6%)
COPD	40 (30.1%)
Cystic fibrosis	13 (9.8%)
Scleroderma	12 (9.0%)
Sarcoidosis	4 (3.0%)
Pulmonary hypertension	3 (2.3%)
Other	15 (11.3%)
Induction agent, n (%)	
Alemtuzumab	89 (66.9%)
Basiliximab	44 (33.1%)
Alive at 1 y posttransplant, n (%)	120 (90.2%)

AA, African American.

**TABLE 2.**

#### Pathogens causing pneumonia in the 1st year post-LT

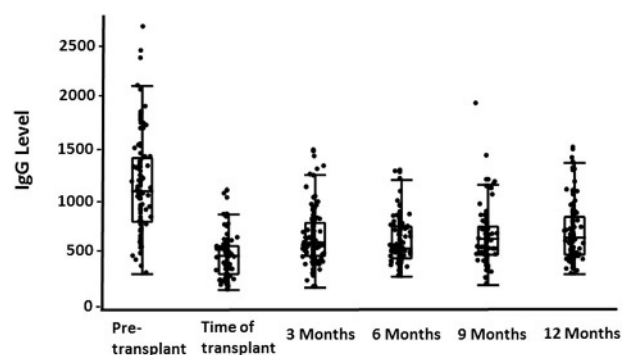
Organism	Occurrences
CMV	5
<i>Streptococcus pneumoniae</i>	1
<i>Klebsiella pneumoniae</i>	7
Rhinovirus	1
Enterovirus	1
<i>Pseudomonas aeruginosa</i>	17
<i>Staphylococcal aureus</i>	9
<i>Alcaligenes</i>	4
<i>Stenotrophomonas maltophilia</i>	5
<i>Legionella pneumophila</i>	3
<i>Aspergillus (various)</i>	3
<i>Acid fast bacilli (unknown type)</i>	1
<i>Escherichia coli</i>	1
<i>Enterococcus</i>	3
<i>Burkholderia cepacia</i>	1
Influenza	2
<i>Streptococcus viridans</i>	1
<i>Acinetobacter</i>	2
Unknown	11

3, 6, 9, and 12 months posttransplant, the percentages were 7.4%, 7.5%, 8.9%, and 6.3%, respectively. Severe HGG at the time of transplant was not associated with postoperative ICU, hospitalization, ventilation days, and CPB/ECMO or pretransplant prednisone dose ( $P = 0.66$ ). Interestingly, fewer than 30% protective pretransplant pneumococcal antibody levels were significantly related to severe HGG at all time points ( $P = 0.0006$ ). In addition, those with COPD as a reason for transplant were more likely to have severe HGG at the time of transplant ( $P = 0.001$ ) and lower pretransplant IgG levels when compared with all other subjects ( $P < 0.0001$ ).

Females were nearly significantly more likely to have severe HGG at any time ( $P = 0.052$ ). Pretransplant IgG levels correlated strongly with IgG level at all time points ( $P < 0.0001$  except at 1-year IgG level  $P = 0.001$ ).

We found that 43 patients were on prednisone before LT with median dose of 10 mg (IQR, 10–15). The pretransplant prednisone dose did not relate to severe HGG before or after LT and was weakly associated with pretransplant IgG level ( $\rho = -0.25$ ;  $P = 0.01$ ) and posttransplant IgG level at 3 months ( $\rho = -0.18$ ,  $P = 0.046$ ).

At the time of transplant, there was no difference in IgG levels between subjects receiving either alemtuzumab or basiliximab



**FIGURE 1.** Pretransplant and posttransplant IgG values.

**TABLE 3.**  
IgG levels pretransplant and posttransplant levels

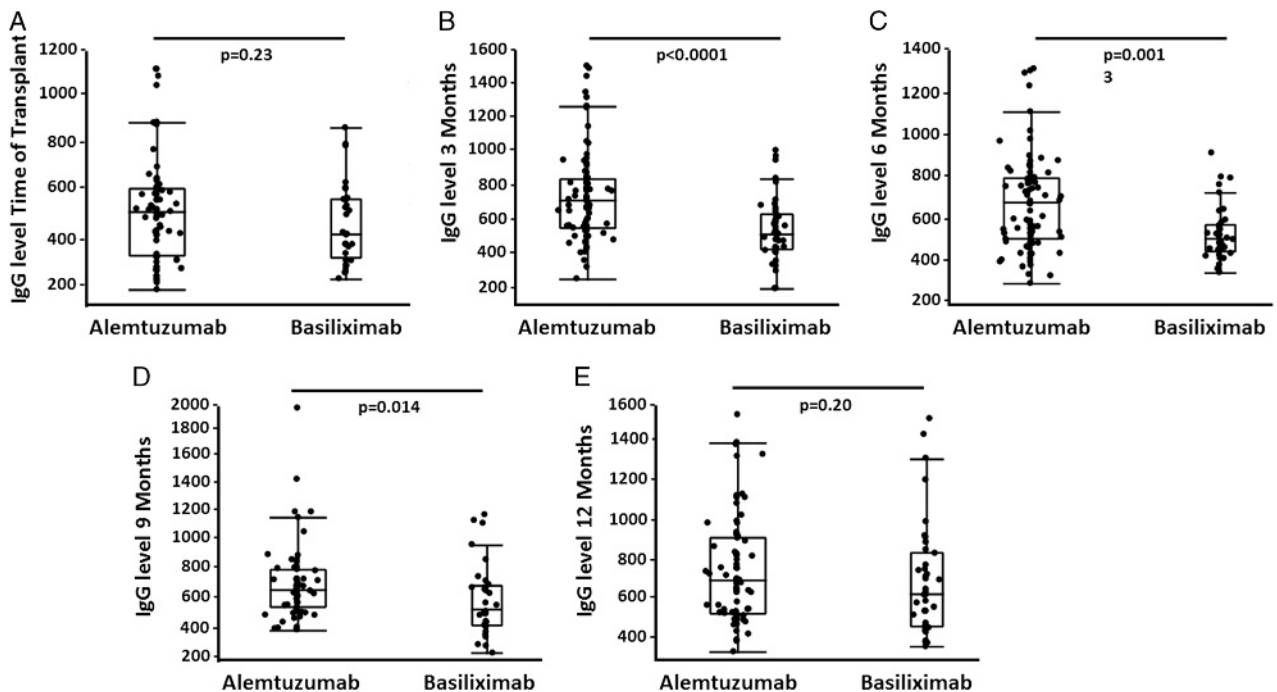
Severe<400; mild = 400-700; normal >700 mg/dL		IgG level (%)
Pretransplant	Normal	85.1
	Mild	12.8
	Severe	2.1
Time of transplant	Normal	10.9
	Mild	56.4
	Severe	32.7
3 mo Posttransplant	Normal	39.3
	Mild	53.3
	Severe	7.4
6 mo Posttransplant	Normal	36.7
	Mild	55.8
	Severe	7.5
9 mo Posttransplant	Normal	37.6
	Mild	53.4
	Severe	8.9
12 mo Posttransplant	Normal	43.8
	Mild	50.0
	Severe	6.3

as induction agents (Figure 2,  $P = 0.23$ ). Those that received basiliximab as the induction agent had lower IgG levels at 3, 6, and 9 months (Figure 2;  $P < 0.0001$ ,  $P = 0.0003$ ,  $P = 0.014$ , respectively) compared with the alemtuzumab group, although this finding was not present at 12 months posttransplant ( $P = 0.20$ ). The induction agent had no relationship to the incidence or number of days with pneumonia ( $P = 0.55$  and  $0.64$ , respectively, data not shown). The patients who received basiliximab induction were on higher doses of prednisone and MMF at 3, 6, 9, and 12 months compared with the alemtuzumab group. The difference in prednisone dose was most pronounced at

3 and 6 months posttransplant. The patients in the alemtuzumab group had lower lymphocyte levels compared with the basiliximab group at all time points (Table 4). There was no relationship or correlation of IgG levels at any time related to treatment with acute steroid courses (data not shown), RATG, and CMV viremia.

**Effect of IgG Levels on Infectious Outcomes and Mortality**

Overall, the incidence and number of days of pneumonia did not differ significantly in those with severe HGG at the time of transplant or at any time posttransplant ( $P = 0.21$  for both outcomes) (Figure 3) compared with those with mild HGG or normal IgG levels(data not shown). However, those with severe HGG at any time during the first year required more total antibiotic courses (Figure 4,  $P = 0.02$ ). Given the relationship between antibiotic courses but not the incidence or days of pneumonia with regards to IgG levels, we sought to further analyze these findings in more detail. We found that subjects who had 2 or more pneumonias in the year after transplant were more likely to have had severe HGG at some point during that year (Figure 5,  $P = 0.02$ ) compared with the subjects with IgG greater than 400 mg/dL. We then performed simple and multiple regressions to determine variables that most closely predicted the presence of severe HGG. Backward stepwise elimination provided a model using both the disease as a reason for transplant and the induction agent used that was most predictive of severe HGG (Table 5,  $P = 0.005$ ). In addition, we were interested in variables that might predict the total days of pneumonia, a commonly used infectious outcome in immunodeficiency studies. Using a similar approach to above, we found that the combination of age, presence of severe HGG at any time, and number of acute steroid courses was most predictive of total days of pneumonia (Table 6,  $P = 0.0001$ ).



**FIGURE 2.** Relationship between IgG level and induction agents.



**TABLE 4.****Immunosuppressant doses, levels, and lymphocyte and WBC counts**

	3 Months		6 Months		9 Months		12 Months	
	A	B	A	B	A	B	A	B
Prednisone, mg	5 <sup>a</sup> (5-5)	15 (10-20)	5 <sup>a</sup> (5-5)	10 (5.75-10)	5 <sup>a</sup> (5-5)	7.5 (5-10)	5 <sup>a</sup> (5-5)	5 (5-10)
MMF, mg	1500 <sup>a</sup> (1000-1500)	2000 (1500-2000)	1500 <sup>a</sup> (1000-1500)	2000 (1000-2000)	1500 <sup>a</sup> (1000-1500)	2000 (1000-2000)	1500 <sup>a</sup> (1000-1750)	2000 (1500-2000)
Tacrolimus, mg	4 (2-6)	2.5 (2-5.8)	4 (2-6)	3.25 (1.4-6.1)	5.5 (3-8.9)	3.5 (2-8)	5 <sup>a</sup> (3-10)	3.3 (2.5-5)
Tacrolimus level	11.6 (9.2-15)	12.7 (8.8-16.3)	10.5 (8.6-13.6)	11.2 (7.6-15.9)	10.1 (8.6-12.3)	9.4 (8.0-11.1)	9.8 (6.9-12.9)	11.4 (9.4-13.4)
CSP, mg	225 (200-387.5)	250 (200-318.8)	225 (175-350)	212.5 (200-250)	250 (200-337.5)	225 (187.5-275)	287.5 (200-381.3)	237.5 (156.3-293.8)
CSP level	232 (108-359)	210 (142-411)	202 (172.8-376.8)	197.5 (114-253.8)	200 (129-259)	186 (119-239)	192 (163.5-242)	192.5 (110-280)
WBC count ( $\times 10^3/\mu\text{L}$ )	4.1 <sup>a</sup> (2.7-5.4)	5.3 (3.4-7.9)	4.3 (3.1-5.95)	4.3 (3.1-6.5)	4.4 (2.85-5.45)	3.95 (3.2-4.98)	4.7 (3.5-6.8)	4.5 (3.3-5.9)
Lymphocyte count ( $\times 10^3/\text{mL}$ )	0.19 <sup>a</sup> (0.07-0.4)	0.5 (0.21-1.1)	0.23 <sup>a</sup> (0.2-0.4)	0.7 (0.43-1.11)	0.3 <sup>a</sup> (0.1-0.3)	0.69 (0.37-0.98)	0.37 <sup>a</sup> (0.2-0.6)	0.78 (0.43-1.35)

All values represented as median (IQR).

<sup>a</sup>  $P < 0.05$  when compared between induction agents at the same time point.

A, alemtuzumab; B, basiliximab; CSP, cyclosporine; WBC, white blood cells.

Thirteen (9.7%) subjects died during the first year posttransplant (Table 7). One-year mortality was associated with lower IgG levels at 3 months posttransplant ( $P = 0.04$ ). This relationship was absent at the time of transplantation and all other time points ( $P = 0.18$ , data not shown). We further explored this finding and found that the pretransplant and 3-month prednisone dose correlated with lower IgG level at 3 months. Absolute lymphocyte count at 3 months was lower in those patients with 2 or more pneumonias ( $P = 0.02$ ). We have also looked at the use of CPB and ECMO during transplant surgery, induction regimens, ventilation days, ICU days after surgery, and hospitalization days after surgery and have found that none of these variables were associated with 1-year mortality. Of note, pre-LT HGG did not predict infection or 1-year mortality.

### Effect of IgG Levels on Acute Rejection

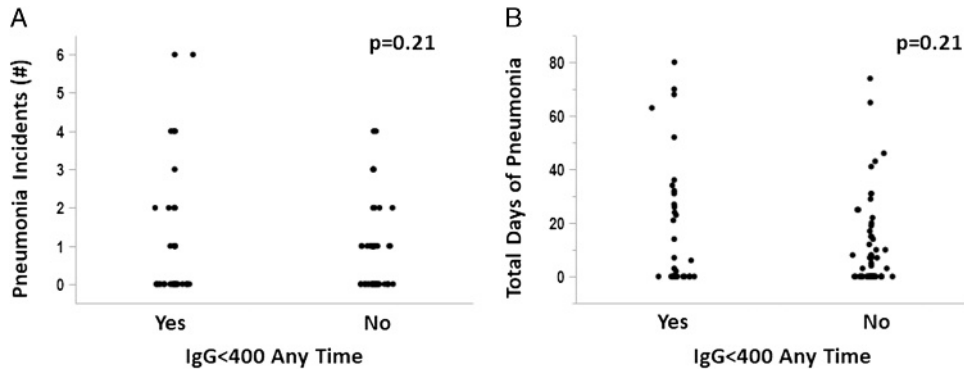
We found no relationship between the presence of severe HGG, mild to moderate HGG, or normal IgG level and the occurrence of ACR, regardless of whether ACR was characterized as mild/minimal or moderate/severe (data not shown). However, IgG levels at 9 months negatively correlated with total number of ACR episodes ( $P = 0.008$ , spearman's  $\rho = -0.26$ ). There was also no relation to humoral rejection.

### IG Replacement Therapy

Immunoglobulin replacement therapy (IGRT) at 400 mg/kg (current body weight) monthly dose was administered to select patients with HGG (IGG  $< 500$  mg/dL) who consented to treatment or at the discretion of a treating physician. Seventy-eight subjects (58.6%) received IGRT at some point after transplant (median, 1; range, 0-8). Of 78 subjects, no patients received regularly scheduled IGRT for 12 months, 31 received 1 month of IGRT and 21 received 2 months of IGRT. Three patients received 6 months of IGRT and 2 patients received 7 to 8 months of IGRT. Those subjects with 2 or more pneumonias were more likely to receive IGRT. There was no difference in days or incidence of pneumonias whether the subjects received IGRT or not (data not shown).

## DISCUSSION

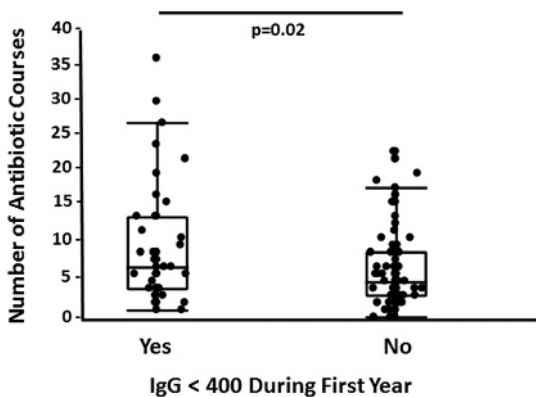
Our study is the largest single-center prospective study of HGG after LT in the first year posttransplantation. We report for the first time the prospective serial IgG levels before transplant, at the time of transplant, and then every 3 months in the first year posttransplantation. Unlike previously published LT studies, we found that median IgG level decreased significantly immediately after LT and remained decreased at all points during the first year post-LT. Our data show that the highest percentage of severe HGG occurred immediately after LT (32.4%). We hypothesize that the high prevalence of severe HGG immediately after transplant could be related to a lower pretransplant IgG level, baseline patient's inflammatory condition, the use of an induction agent, mechanical losses, and third spacing with a capillary leak syndrome that can be seen in CPB surgery.<sup>7-10</sup> However, in our study, we did not find an association between severe HGG and CPB/ECMO use. After the initial posttransplant measurement, severe HGG improved and remained below 10% at all subsequent time points. Incidence of severe HGG in our study at 3 to 12 months is slightly lower than what was reported in other studies. Goldfarb et al<sup>11</sup> reported that the mean time



**FIGURE 3.** Relationship between severe HGG and pneumonias.

to the lowest IgG level was 29.6 months and severe HGG was present in 37% of LT recipients; however, they started to collect IgG levels late in their study. Yip et al<sup>12</sup> reported that the median times from transplantation to diagnosis of mild and severe HGG were 33 and 190 days and severe HGG was found in 15% of LT recipients. Additionally, they noted there was a trend of decreasing IgG level with a longer duration from LT which we did not observe in our study. Kawut et al<sup>13</sup> assessed IgG levels at 10 months posttransplantation and severe HGG was seen in 14% of LT recipients. Another small study reported decreased IgA and IgG levels at 3 months posttransplant.<sup>14</sup> Of note, 2 retrospective studies<sup>12,13</sup> do not comment whether IGRT was administered at any point during the study and in 1 study,<sup>11</sup> IGRT was administered at physician discretion.

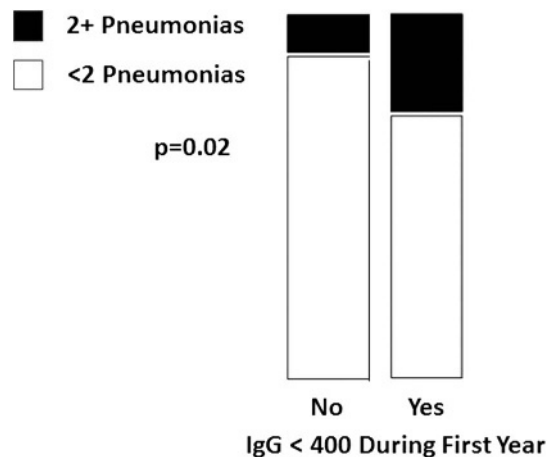
It is noteworthy that all patients in our study received alemtuzumab or basiliximab as induction agents and majority of our patient population was on MMF and tacrolimus as part of their immunosuppressive regimen (25% of patients were on cyclosporine instead of tacrolimus). Conversely, daclizumab was used as the induction agent in the studies by Yip et al and Kawut et al.<sup>12,13</sup> Goldfarb et al<sup>11</sup> did not use an induction agent and they used cyclosporine and azathioprine for immunosuppression. Moreover, in the study by Yip et al,<sup>12</sup> only 15% of patients were on MMF, and the remainder were on azathioprine and tacrolimus. Although Yip et al found that the patients taking MMF had significantly lower IgG levels, Kawut et al<sup>13</sup> did not find this association. In the study by Kawut et al, it was not reported how many patients were on azathioprine versus MMF in conjunction with tacrolimus. We also did not find an association between cyclosporine dose/level and IgG level.



**FIGURE 4.** Relationship between IgG levels and antibiotic courses.

We report a novel observation seen both in univariate and multivariate analyses that HGG is more likely to be associated with the use of basiliximab induction regimen compared with alemtuzumab. However, the patients in the basiliximab group were on the higher doses of MMF and prednisone which likely contributed to the difference in IgG level between the 2 groups. Although other studies have suggested that impact of chronic steroid dosing on IgG level can be dose-dependent,<sup>15-17</sup> Kawut et al<sup>13</sup> did not find that the differences in corticosteroid use were associated with severe HGG. In our study, we did not find an association between acute steroid treatments and severe HGG.

We have collected pretransplant pneumococcal antibody levels as part of our study. Unfortunately, posttransplant pneumococcal antibody levels were not collected. We report a novel finding that those patients with pretransplant pneumococcal antibody levels that were less than 30% protective were more likely to have posttransplant severe HGG suggesting an immunologic predisposition to severe HGG. It is noteworthy that diagnostic use of pneumococcal antibody levels is fraught with challenges in both nonimmunosuppressed and immunosuppressed populations.<sup>18,19</sup> Several studies have demonstrated that amnestic vaccine response to vaccination is suboptimal in patients on immunosuppressive medications.<sup>20-22</sup> Furthermore, as stated in the vaccination practice parameter, “secondary immunodeficiencies might affect antigen-specific responses and diminish the response to the pneumococcal vaccine.”<sup>18</sup> This has been our unreported experience as well



**FIGURE 5.** Relationship between severe HGG and recurrent pneumonias.

**TABLE 5.**  
Simple and multiple regressions using severe HGG as the independent variable

Simple logistic regression			
Dependent variables	Independent variable	Individual <i>P</i>	Overall <i>P</i>
IgG < 400 at any time	Age	0.64	
	Gender	0.05	
	Race	0.04	
	Disease	0.01	
	CMV viremia	0.58	
	Induction agent	0.08	
	Pneumonia Incidents	0.04	
	Days of Pneumonia	0.04	
	Number of antibiotic courses	0.02	
	ACR	0.57	
	No. steroid courses	0.95	
Multiple logistic regression IgG < 400 at any time	Sex	0.16	0.008
	Race	0.13	
	Disease	0.16	
	Induction	0.09	
	Pneumonia incidents	0.97	
	Days of pneumonia	0.71	
	No. antibiotic courses	0.51	
Backward stepwise elimination IgG < 400 at any time	Disease	0.008	0.005
	Induction	0.04	

from a separate LT cohort (not part of this study) where there was a significant decrease of posttransplant pneumococcal antibody levels. We postulate that transplant recipients exhibit

**TABLE 6.**  
Simple and multiple regressions using days of pneumonia as the independent variable

Simple linear regression			
Dependent variable	Independent variable	Individual <i>P</i>	Overall <i>P</i>
Days of pneumonia	Age	0.02	
	Sex	0.21	
	Race	0.94	
	Disease	0.15	
	CMV viremia	0.38	
	Induction agent	0.79	
	Ig < 400 at any time	0.04	
	Use of IVIG	0.40	
	ACR	0.65	
	No. steroid courses	0.001	
	Multiple linear regression Days of pneumonia	Age	0.08
Disease		0.28	
IgG < 400 at any time		0.13	
No. steroid courses		0.0003	
Backward stepwise elimination Days of pneumonia	Age	0.02	0.0001
	IgG < 400 at any time	0.03	
	No. steroid courses	0.0008	

**TABLE 7.**  
Causes of death post-LT

Causes of death	Months after transplant
PTLD	5
Pneumonia and respiratory failure	8
Allograft failure and renal failure	7
Pneumonia with malignancy	12
Pneumonia	8
Unknown	4
Pneumonia	3
Cryptogenic cirrhosis	6
Pneumonia, TTP, sepsis	9
Pneumonia and septic shock	5
Allograft failure	1.5
Respiratory failure	6
Hyperammonemia and respiratory failure	3

PTLD, posttransplant lymphoproliferative disease; TTP, thrombotic thrombocytopenic purpura.

the memory phenotype of pneumococcal antibody deficiency with nondurable vaccine response secondary to immunosuppression.<sup>18,23</sup> For all these reasons, the antibody response to pneumococcal vaccination was recently reported to be 7th in the order of importance among immunologists when deciding whether to treat secondary HGG with IGRT.<sup>24</sup>

Previous studies have reported that patients with emphysema are more likely to develop severe HGG. Yip et al<sup>12</sup> reported that pretransplant IgG level was a predictor of posttransplant IgG level and the diagnosis of COPD was a predictor of a lower pretransplant IgG level. Kawut et al<sup>13</sup> found that emphysema and female sex were associated with severe HGG. Similar to these studies, we have also found that patients with COPD and women were more likely to develop severe HGG as well as that lower pretransplant IgG level was associated with lower posttransplant IgG level. The mechanism of HGG in COPD remains unknown.

Similar to other groups, we have found no significant association between IgG level and acute rejection.<sup>12,13</sup>

In our study, we did not find a difference in the incidence or days with pneumonia in patients with mild/severe HGG and normal IgG level. This is similar to the findings published by Yip et al and different from Kawut et al and Goldfarb et al who reported an increased risk of pneumonia in patients with severe HGG and mild/severe HGG, respectively. However, we are first to report that those patients with 2 or more pneumonias were more likely to have severe HGG compared with the patients with IgG level above 400. We believe that this might represent an important finding as it may identify a subgroup of patients who are at risk for recurrent pneumonias and may benefit from IGRT. Furthermore, unlike Yip et al, we found that the patients with severe HGG received more antibiotic courses which may reflect an overall higher infectious burden in this patient population. In our multivariate model, we found that an older age, severe HGG, and the number of steroid courses were predictors of an increased number of days with pneumonia. Finally, we found no association between CMV viremia and IgG level similar to the studies by Yip et al and Kawut et al.

We have identified the pathogens causing pneumonias in our patient population and the types of pathogens are consistent with impaired T and B lymphocyte function. Although

encapsulated organisms have been traditionally associated with antibody deficiency, recent studies of infections in patients on immunosuppressive medications targeting B lymphocytes and humoral immunity (such as rituximab) have demonstrated that the spectrum of bacterial infections is much wider.<sup>25,26</sup>

As reported in prior retrospective studies, we have identified that lower IgG level is associated with decreased survival. In our study, this association was seen at 3 months posttransplantation and not beyond that time-point; this may reflect survivor bias insofar as only those patients who survived continued to have their IgG levels available for analysis. Additionally, 1-year mortality was associated with mild rather than severe HGG at 3 months posttransplant. We have performed additional analysis of other relevant variables and found that the pretransplant and 3-month prednisone dose correlated with lower IgG level at 3 months suggesting an impact of steroid dosing on the IgG level. However, these variables were not associated with 1-year mortality. These findings will need further study.

Our study has a few limitations. First, it is a single-center study which may limit the applicability of our findings. Second, our induction immunosuppression regimen may be specific to our center only. Third, we cannot exclude some component of selection bias since not all transplant patients consented to be in the study and majority of patients were Caucasian. Fourth, due to observational and real-world nature of our study, over half the patients received IGRT during the 1st year posttransplantation. Previous studies had suggested that short-term IGRT might be effective in improving clinical outcomes in solid organ transplant patients, whereas recent studies indicated that short-term IGRT was not effective in LT patient population.<sup>27-30</sup> Our observational study did not restrict IGRT use, and it was left to the discretion of a treating physician whether to prescribe IGRT in a real-world setting. Additionally, ethical and likely IRB limitations would have made it difficult to restrict IGRT use in high-risk LT patients. This observational study was not designed to evaluate the efficacy of IGRT. In our opinion, short-term IGRT would not have provided significant therapeutic prophylaxis/benefit or impact serial IgG levels over the 12-month study period. For example, the median half-life of IVIG used in our institution is 32 days and most treated subjects in our study received only 1 to 2 months of IGRT. It is noteworthy that only long-term IGRT has been used in primary immunodeficiency conditions. We are currently analyzing data on regularly scheduled IGRT use for HGG in LT recipients which will be reported in a separate manuscript. Fifth, the technical losses might be contributing to the higher prevalence of HGG at the time of transplant. Interestingly, ECMO and CPB use had no impact on IgG levels. After excluding IgG levels at the time of transplant we have found that severe HGG tended to be associated with antibiotic courses ( $P = 0.07$ ) and 2 or more pneumonias ( $P = 0.09$ ). These findings in our opinion remain clinically significant considering that we are not certain as to the true prevalence of immunologic versus nonimmunologic HGG immediately posttransplant and the impact of induction in the first 1 to 2 months after transplant. Sixth, IgG level can decrease acutely in the setting of acute infection and rebound to normal/higher levels after the infection has resolved, potentially complicating the analysis of an association between

HGG and recurrent infections. Finally, we have found the increased incidence of pneumonias in severe HGG despite some patients receiving IGRT which in our opinion only strengthens our findings. We cannot rule out that additional relevant observations may have been noted if no patients had received IGRT.

In conclusion, the clinical significance of HGG and reliable predictors of infections have been difficult to elucidate in immunodeficiency conditions. Clinical presentation in conjunction with laboratory studies has historically provided the necessary context for making treatment decisions in secondary immunodeficiency conditions. Most immunologists will treat secondary HGG only if associated with recurrent infections as shown by Edgar et al.<sup>24</sup> In the latest immunodeficiency practice parameter IGRT is recommended for patients with HGG after transplantation.<sup>2</sup> In our large observational prospective study, we aimed to better characterize the natural course of HGG in the 1st year postlung transplantation and identify the patients at risk for infections with secondary HGG. We show that severe HGG is associated with 2 or more pneumonias and more antibiotic use. We have identified pre and posttransplant risk factors for severe HGG and the patients who might be at risk for pneumonia. It is our opinion that the LT recipients with severe HGG and recurrent pneumonias should be treated with regularly scheduled IGRT as the benefits outweigh the risks in this high-risk patient population. The patients with HGG and no infections should be monitored and not treated unless they develop recurrent infections. Additional randomized studies should be performed to further evaluate the effect of IGRT on HGG in LT recipients.

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