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ORIGINAL ARTICLE

Risk Factors of Pneumonia in Primary Antibody Deficiency Patients Receiving Immunoglobulin Therapy: Data from the US Immunodeficiency Network (USIDNET)

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Abstract

Background Despite immunoglobulin replacement (IgRT) therapy, some patients with primary antibody deficiency (PAD) continue to develop respiratory infections. Recurrent and severe respiratory infections, particularly pneumonia, can lead to significant morbidity and mortality. Therefore, we sought to determine the risk factors of developing pneumonia in PAD patients, already receiving IgRT.

Methods We evaluated clinical and laboratory features of PAD patients enrolled in the US Immune Deficiency Network (USIDNET) registry by April 2017. Patients were included if they met the following criteria: (1) PAD diagnosis (common variable immunodeficiency (CVID), agammaglobulinemia, hypogammaglobinemia, and specific antibody deficiency (SAD) and (2) available data on infections before and after IgRT. Patients were excluded if they were not receiving IgRT, or if no pre/post infections data were available. Descriptive and multivariable logistic regression analyses were used to identify factors associated with pneumonia post-IgRT.

Results A total of 1232 patients met the inclusion criteria. Following IgRT, 218 patients (17.7%) were reported to have at least one pneumonia episode. Using multivariate logistic regression analysis, we found a statistically significant increased risk of pneumonia in patients with asthma (OR: 2.55, 95% CI (1.69–3.85), $p < 0.001$) bronchiectasis (OR: 3.94, 95% CI (2.29–6.80), $p < 0.001$), interstitial lung disease (ILD) (OR: 3.28, 95%CI (1.43–7.56), $p < 0.005$), splenomegaly (OR: 2.02, 95%CI (1.08–3.76), $p < 0.027$), allergies (OR: 2.44, 95% CI [1.44–4.13], $p = 0.001$), and patients who were not on immunosuppressives (OR: 1.61; 95%CI [1.06–2.46]; $p = 0.027$). For every 50 unit increase in IgA, the odds of reporting pneumonia post IgRT decreased (OR: 0.86, 95% CI [0.73–1.02], $p = 0.062$).

Infectious organisms were reported in 35 of 218 patients who reported pneumonia after IgRT. *Haemophilus influenzae* was the most frequently reported ($n = 11$, 31.43%), followed by *Streptococcus pneumoniae* ($n = 7$, 20.00%).

Conclusion Our findings suggest PAD patients with chronic and structural lung disease, splenomegaly, and allergies were associated with persistent pneumonia. However, our study is limited by the cross-sectional nature of the USIDNET database and limited longitudinal data. Further studies are warranted to identify susceptible causes and explore targeted solutions for prevention and associated morbidity and mortality.

Clinical Implications Patients with primary antibody deficiency with structural lung disease, allergies, and splenomegaly are associated with persistent pneumonia post-IgRT.

Keywords Specific antibody deficiency · common variable immunodeficiency · hypogammaglobulinemia · agammaglobulinemia · upper respiratory infection · *streptococcus pneumonia* · *haemophilus influenzae* · immunoglobulin replacement therapy

Abbreviations

AID	Deficiency activation-induced cytidine deaminase deficiency
aOR	Adjusted odds ratio
BTK	Bruton's tyrosine kinase
CD40L	CD40 ligand

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CVID	Common variable immunodeficiency
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
GLILD	Granuloma, interstitial lung disease
HIGM	Hyper-IgM syndrome
IG	Immunoglobulin
IgRT	Immunoglobulin replacement therapy
IM	Intramuscular
IQR	Interquartile range
IRB	Institutional Review Board
IV	Intravenous
IVIG	Intravenous immunoglobulin
OR	Odds ratio
PAD	Primary antibody deficiency
SAD	Specific antibody deficiency
SD	Standard deviation
SC	Subcutaneous
SCIG	Subcutaneous immunoglobulin
TACI Deficiency	Transmembrane activator and CAML interactor deficiency
USIDNET	United States Immunodeficiency Network
XLA	X-linked agammaglobulinemia

Introduction

Primary antibody deficiency disorders (PADs) are humoral immune deficits characterized by defective immunoglobulin production and function and recurrent respiratory and gastrointestinal tract infections that significantly contribute to morbidity and mortality [1–3]. Recurrent and severe respiratory infections have been associated with poor quality of life in PAD [4, 5] and could lead to chronic, irreversible lung disease (e.g., bronchiectasis) [6–9], even in those with subclinical infections [10].

Treatment with immunoglobulin replacement therapy (IgRT) via intravenous (IV) or subcutaneous (SC) routes is used to reduce the incidence of infections [11]. However, many patients with PAD continue to have persistent respiratory infections [12–14]. There is a wide variation in the use of prophylactic antibiotics for patients with PAD, with some studies showing minimal efficacy for those patients already receiving IgRT [15, 16].

Given the challenge and importance of reducing the risk of recurrent respiratory infection, particularly pneumonia, in patients with PAD, we aimed in this study to identify the pathogens responsible for pneumonia in patients with PAD after initiation of IgRT and to explore factors that may predict risks of developing pneumonia after the initiation of IgRT.

Methods

Data Sources

Data for analyses were acquired in a de-identified format from the US Immunodeficiency Network (USIDNET) registry, a research consortium established to advance scientific research on inborn errors of immunity. The study was approved by the USIDNET Steering Committee and the Baylor College of Medicine Institutional Review Board (IRB). The registry is populated by participating clinician-investigators at thirty-nine academic institutions in the USA and Canada. Data in the registry include demographic, clinical, and laboratory information abstracted and entered by the investigators and medical records submitted by participants, which are confirmed and entered by the investigator. In April 2017, we queried the USIDNET patient registry for demographic, clinical, and laboratory data, including immunoglobulin levels, infectious pathogens, antibiotic therapy, and immunoglobulin therapies.

Patients were included if they had a confirmed PAD diagnosis of common variable immune disorder (CVID), agammaglobulinemia, specific antibody deficiency (SAD), hyper-IgM syndrome, excluding CD40L patients (HIGM), and hypogammaglobulinemia (unknown cause and no listed genetic defect). In addition, we excluded patients if they were not receiving IgRT or if pre/post infections data were unavailable.

Statistical Analysis

Categorical variables were summarized using frequencies and percentages, and continuous measures were summarized using mean ± standard deviation (SD), or median with interquartile ranges (IQRs).

Univariate comparisons were made using the *t*-test, chi-square test, Fisher's exact test, and Wilcoxon's rank-sum tests. Variables with a $p < 0.25$ were considered for inclusion in an exploratory multivariate logistic regression model.

A backward stepwise selection method was used to build the multivariable regression model. First, all variables were entered into a preliminary model and were reviewed. Then, the highest *p*-value was eliminated, and the model was re-run. This was repeated at every step until all *p*-values were significant ($p < 0.1$) [17].

Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated for each predictor to examine their contribution to the likelihood of having persistent respiratory infection after initiating IgRT. All data were analyzed using (Stata/IC, Version 12.11).

Results

Demographics and Clinical Characteristics of the Baseline Cohort

At the time of our query (April 2017), the USIDNET database included 2230 patients with PAD. Out of those, $n = 1232$ patients with a confirmed diagnosis of PAD were treated with IgRT and had available information on infections post-IgRT. The mean age at PI diagnosis was 15.7 years (0–84). Most patients (82.87%) identified as Caucasian, and 35% were female. The most-reported diagnosis was CVID (70.62%). Complete patients' characteristics are summarized in Table 1s. Lung disease (34.01%) was the most commonly reported comorbidity, including asthma (22.32%) and bronchiectasis (7.79%), followed by hematological autoimmune disease and gastrointestinal disease (24.43% and 20.05%, respectively). Out of the 1232 included in the study, 159 patients were reported to be receiving prophylactic antibiotics. Patients' comorbidities and immune phenotypes are summarized in Table 2s and Table 3s, respectively.

Post-treatment Pneumonia and Causative Pathogens

Pneumonia was reported in 218 patients after initiating IgRT (Table 1). Males reported a higher post-IgRT pneumonia frequency compared to females (60.09% vs. 39.91%). Females had a later diagnosis in this cohort with a median age of 28 years compared to median age of 7 years for males. A PAD diagnosis of CVID (70.64.1%) was most reported, followed by hypogammaglobinemia (24.77%) (Table 1). Lung disease was the most common comorbidity (57.80%) (Table 2). Thirty-five out of 218 patients who reported pneumonia after IgRT also reported the organism of infection that caused their pneumonia. *Haemophilus influenzae* was the most frequently reported ($n = 11$, 31.43%) followed by *Streptococcus pneumoniae* ($n = 7$, 20.00%). Thirty-five patients reported receiving prophylactic antibiotics post-IgRT. A list of reported prophylactic antibiotics is summarized in Table 4s.

Immunoglobulin Levels

We then evaluated the impact of immunoglobulin levels on post-IgRT infection. Of note, Ig levels were provided one-time value. There was no available data on when those values were reported in relation to IgRT. Patients' immunological data are summarized in Table 3.

Table 1 Patient characteristics: patients with pneumonia Post IgG therapy ($n = 218$)

	Number	Percent
Characteristic		
Sex		
Female	87	39.91%
Male	131	60.09%
Age at PI diagnosis (years)		
All patients, median (range)	13.1	(0.1–70)
Females	28	(0.8–70)
Males	7	(0.1–63)
Time in years from symptom onset to diagnosis, median (range)		
PAD diagnosis		
CVID	154	70.64%
Hypogammaglobinemia (including XLA, BTK)	54	24.77%
Specific antibody deficiency	7	3.21%
Hyper-IgM (excluding CD40L)	3	1.38%
Race/ethnicity		
White or Caucasian	164	75.23%
Black or African American	12	5.50%
Asian or Pacific Islander	1	0.46%
Other or more than one race	2	0.92%
American Indian/Native American	1	0.46%
Unknown	38	17.38%
Route of IgRT		
Intravenous	124	56.88%
Subcutaneous	55	25.23%
Unknown	38	17.43%
Intramuscular	1	0.46%

Abbreviations: CD40L CD40 ligand, *CVID* common variable immunodeficiency, *XLA* X-linked agammaglobulinemia, *BTK* Bruton tyrosine kinase, *COPD* chronic obstructive pulmonary disease, *Hyper-IgM* hyper-IgM syndrome, *IM* intramuscular, *IV* intravenous; *SC* subcutaneous, *PAD* primary antibody deficiency, *PI* primary immunodeficiency, *IgRT* immunoglobulin replacement therapy

Multivariate Analysis for Pneumonia after IgRT Treatment in PAD Patients

To determine which variables to consider for building the multivariate logistic regression model for predicting pneumonia after beginning IgRT treatment, a univariate analysis was run, and variables with a $p < 0.25$ were considered for the multivariate logistic regression model.

Variables with a p-value of less than 0.25 included IgA (mg/dl—50-unit increments), absolute lymphocyte count (100-unit increments), age 18–26 compared to all other ages, COPD, autoimmune, granulomas, adenopathy, liver disease, EOE, IgRT type (SCIG or IVIG only), prophylactic antibiotics, and PID diagnosis (CVID vs. all others and XLA vs. all others).

Table 2 Patient comorbidities: patients with pneumonia Post IgG therapy ($n=218$)

Comorbidities	Number	Percent
Respiratory		
Lung disease*	126	57.80%
Asthma	73	33.49%
Bronchiectasis	38	17.43%
COPD	17	7.80%
Interstitial lung disease	12	5.50%
Granuloma	8	3.67%
Lung nodules	1	0.46%
Hematological	73	33.49%
Anemia	39	17.89%
Adenopathy	27	12.39%
Thrombocytopenia	19	8.72%
ITP	17	7.80%
Neutropenia	13	5.96%
Pancytopenia	1	0.46%
Gastrointestinal (GI)	47	21.56%
Spleen	27	12.39%
Liver	20	9.17%
IBD	18	8.26%
Abnormal LFTs	6	2.75%
EOE	5	2.29%
Liver failure	5	2.29%
Celiac disease	3	1.38%
PLE	3	1.38%
Other		
Allergies	34	15.60%
Autoimmune	24	11.01%

Abbreviations: COPD chronic obstructive lung disease, *ITP* idiopathic thrombocytopenia purpura, *GI* gastrointestinal disease, *IBD* inflammatory bowel disease, *EOE* eosinophilic esophagitis, *LFTs* liver function test, *PLE* protein-losing enteropathy

*Lung disease not otherwise specified in the database

The backward stepwise selection method was used to build the multivariate model. First, all variables were entered into a preliminary model, and the *p*-values were reviewed. Then, the highest *p*-value was eliminated, and the model was re-run. This continued at each step of the model until all *p*-values were considered significant ($p<0.10$).

During the process of backward stepwise regression, the following variables were eliminated from the final model due to a *p*-value of larger than 0.10: absolute lymphocyte count (100-unit increments), age 18–26 compared to all other ages, COPD, autoimmune, granulomas, adenopathy, liver disease, EOE, IgRT type (SCIG or IVIG only), prophylactic antibiotics, and PID diagnosis (CVID vs. all others and XLA vs. all others).

After performing backward stepwise regression, the final multivariate model included IgA (mg/dl—50-unit increments), bronchiectasis, asthma, hematological, allergies, interstitial lung disease, splenomegaly, and taking immunosuppressives after beginning IgRT treatment.

Below are the predicted outcomes for each variable, summarized in Table 4:

- Bronchiectasis

  Compared to patients who did not report bronchiectasis, patients who did report bronchiectasis had an increase in the odds of reporting pneumonia after IGRT (OR: 3.94, 95% CI [2.29–6.79], $p<0.001$) while holding all other variables constant.

- ILD

  Compared to patients who did not report ILD, patients who did report ILD had an increase in the odds of reporting pneumonia after IGRT (OR: 3.28, 95% CI [1.43–7.56], $p=0.005$), while holding all other variables constant.

- Asthma

  Compared to patients who did not report asthma, patients who did report asthma had an increase in the

Table 3 Immune phenotype: patients with pneumonia Post IgG therapy ($n=218$)

Variables	Immunoglobulins mg/dL			Lymphocyte count (μL)
	IgA	IgG*	IgM	
Immunoglobulin overall median range	9.495 (0–667)	960 (22–1467)	21 (0–645)	1815 (200–10,098)
CVID	15 (0–667)	972.5 (109–1467)	28.5 (0–645)	1700 (200–7958)
Hyper-IgM (excluding CD40L)	6.99 (0–7)	–	52 (20–509)	8600 (3100–9000)
Specific antibody deficiency	73 (6–430.8)	1227.5 (1120–1335)	58.65 (20–159)	1435.2 (900–6539)
Hypogammaglobinemia (including XLA, BTK)	7 (0–97)	145 (22–1270)	9 (0–91.6)	2800 (700–10,098)

Abbreviations: CD40L CD40 ligand, *CVID* common variable immunodeficiency, *XLA* X-linked agammaglobulinemia, *BTK* Bruton tyrosine kinase; *COPD* chronic obstructive pulmonary disease, *Hyper-IgM* hyper-IgM syndrome, *GLILD* granulomatous and lymphocytic interstitial lung disease, *IM* intramuscular, *IV* intravenous, *SC* subcutaneous, *PAD* primary antibody deficiency

*IgG taken close to treatment ($n=43$)

Table 4 Factors that affect the risk of persistent infections post immunoglobulin replacement therapy

Risk factor	Adjusted OR (95% CI)	*p*-values
Bronchiectasis	3.94 (2.29–6.80)	< 0.001
ILD	3.28 (1.43–7.56)	0.005
Asthma	2.55 (1.69–3.85)	< 0.001
Allergies	2.44 (1.44–4.13)	0.001
Splenomegaly	2.02 (1.08–3.76)	0.027
Immunosuppressives (yes vs no)	0.62 (0.41–0.95)	0.027
*IgA mg/dL (50-unit increments)	0.86 (0.73–1.02)	0.062
*Hematological	1.44 (0.94–2.20)	0.090

Abbreviations: Area under the curve = 0.7486

*Variables were significant in building the multivariate model to generate the best fit, but did not reach statistical significance as individual variables in the multivariate analysis

XLA X-linked agammaglobulinemia, *ILD* interstitial lung disease, *OR* odds ratio, *CI* confidence interval

odds of reporting pneumonia after IGRT (OR: 2.55, 95% CI [1.69–3.85], $p < 0.001$), while holding all other variables constant.

- Allergies

  Compared to patients who did not report allergies, patients who did report allergies had an increase in the odds of reporting pneumonia after IGRT (OR: 2.44, 95% CI [1.44–4.13], $p = 0.001$), while holding all other variables constant.

- Splenomegaly

  Compared to patients who did not report splenomegaly, patients who did report splenomegaly had an increase in the odds of reporting pneumonia after IGRT (OR: 2.02, 95% CI [1.08–3.76], $p = 0.027$), while holding all other variables constant.

- Immunosuppressives

  Compared to patients who were not on immunosuppressives, the patients who were immunosuppressives had a decrease in the odds of reporting pneumonia after IGRT (OR: 0.62, 95%CI [0.41–0.95]; $p = 0.027$), while holding all other variables constant.

The following 2 variables were significant in building the multivariate model to generate the best fit, but did not reach statistical significance as individual variables in the multivariate analysis:

- Hematological

  Compared to patients who did not report hematological comorbidities, patients who did report hematological comorbidities had an increase in the odds of reporting pneumonia after IGRT (OR: 1.44, 95% CI [0.94–2.20], $p = 0.090$), while holding all other variables constant.

- IgA (mg/dL)

  For every 50 unit increase in IgA, the odds of reporting pneumonia post-IgRT decreased significantly (OR: 0.86, 95% CI [0.73–1.02], $p = 0.062$).

Discussion

This exploratory analysis aimed to identify factors associated with pneumonia in patients with PAD following treatment with IgRT. Persistent respiratory symptoms and complications such as pneumonia pose a significant cause of morbidity and mortality among pediatric and adult patients with inborn errors of immunity [18]. However, its predictors are not well understood. As such, this study provides additional clarity to this challenging problem.

Consistent with previous literature, we have confirmed that *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (hib) are the most common pathogens identified in patients with PAD with respiratory infections [19–21], even after IgRT. Although most commercially available IgRT products contain antibodies to *Streptococcus pneumoniae* and hib, the levels of those specific antibodies vary significantly between products [22, 23], and preparations are not standardized for specific antibody content for the pathogens that most commonly cause infections in patients with inborn errors of immunity [24]. Additionally, the inability to directly transport IgG to mucosal membranes has been postulated to be a risk factor for persistent infections in patients with PAD [16]. Equally important, respiratory viral infections could lead to persistent and severe respiratory infections despite IgRT [25].

From a host perspective, we have identified several significant predictors of pneumonia in patients with PAD after IgRT therapy. Consistent with previous studies, we noted that asthma, bronchiectasis, and interstitial lung disease significantly increased the risk of pneumonia in a patient with PAD despite receiving immunoglobulin replacement therapy [26–29]. Higher IgA serum levels were, in contrast, might be protective.

Furthermore, we show that having a diagnosis of CVID, or hypogammaglobinemia, increased the incidence of pneumonia while on IgGRT. CVID accounted for most patients, and most had chronic lung disease. In a multicenter study by Quinti et al., in patients with CVID, the presence of bronchiectasis was associated with persistent respiratory infections despite IgRT in those with IgA levels < 7 mg/dL and those with persistently IgG trough levels < 400 mg/dL) [14], while

in XLA, bronchiectasis was the only predictor of increased risk of pneumonia following IgRT in the same center [14]. Together, these data raise the need for controlled studies to identify the best approach to prevent persistent infections in patients receiving therapeutic doses of IgRT.

We also found that patients with splenomegaly and hematological complications had higher odds of reporting pneumonia following IgRT. In many cases in patients with CVID, and other antibody deficiency disorders, the non-infectious complications present with multisystem involvement, including lung disease, liver disease, GI disease, and splenomegaly. Those patients are prone to persistent innate and adaptive immune activation, despite IgRT [30, 31].

We hypothesize that chronic immune activation can lead to immune exhaustion, which increases the risk of infections. Therefore, being on immune suppression might be beneficial and even perhaps protective from further infections in these patients.

We found that allergies were associated with increased odds of reporting pneumonia in PAD patients following IgRT. However, previous studies showed that many patients report symptoms of rhinitis and wheezing, despite having low to undetectable IgE levels [32]. Therefore, we hypothesize that allergy symptoms might be due to alternative diagnoses such as upper respiratory infections in those patients.

The main strengths of this study include the use of USIDNET registry data, its large size, and prospective data collection from thirty-nine institutions, and the broad representation of PAD increases our ability to generalize results. Our study was the largest of its kind to evaluate predictors of respiratory infections in patients with PAD. While registries allow the collection of rare diseases, there are limitations in that reporting cases is voluntary, and data might be entered once, or updated as per providers' discretion. Hence, the frequency of infections/year could not be ascertained, as the USIDNET database does not allow for longitudinal study design. In addition, as this was a secondary analysis, due to the nature of the USIDnet database that relies on self-reporting by physicians, we do not have access to patient charts, dosing of IgRT or its timing, and laboratory data such as IgG trough levels, and dosing of IgRT cannot be ascertained. Despite these limitations, our study provides insights on predictors for persistent infections in patients with PAD from both patient and pathogen-related factors.

Conclusion

IgRT significantly reduces but does not eliminate respiratory infections in patients with PAD. In addition, chronic lung disease, splenomegaly, and allergies were associated with an increased risk of post-IgRT pneumonia. At the same time, higher serum IgA levels and immunosuppressive use decreased post-IgRT pneumonia risk.

Our study is limited by the cross-sectional nature of the USIDNET database and limited longitudinal data, particularly the lack of dosing data. Prospective studies exploring targeted solutions for prevention and associated morbidity and mortality are warranted.

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Author Contribution CK and JH performed material preparation, data collection, and analysis. MS and JH wrote the first draft of the manuscript. FK, JM, and RM contributed critical reviews and comments on data analysis, manuscript endpoints, and overall message. CCR, KS, and RF contributed significantly to the USIDNET database (> 10% of patients included). All the authors commented on previous versions of the manuscript. All the authors contributed to the study's conception and design. Finally, all the authors read and approved the final manuscript.

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Data Availability The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability N/A.

Declarations

Ethics Approval The study was approved by the USIDNET Steering Committee and the Baylor College of Medicine Institutional Review Board (IRB).

Consent to Participate N/A.

Consent for Publication N/A.

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