Pneumonia in Primary Antibody Deficiency Patients Receiving Immunoglobulin Therapy, Risk Factors, and Role of Prophylactic Antibiotics: 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, hypogammaglobulinemia, and specific antibody deficiency (SAD). 2) Available data on infections before and after IgRT. Patients were excluded if they were not receiving IgRT, or 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 1286 patients met the inclusion criteria. Following IgRT, 226 patients (17.6%) 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: 1.79, 95% CI [1.20-2.67], $p=0.004$), bronchiectasis (OR: 2.81, 95% CI [1.64-4.80], $p<0.001$), and interstitial lung disease (ILD) (OR: 2.90, 95% CI [1.26-6.70], $p=0.013$). Patients who did not receive prophylactic antibiotics had a much higher risk of pneumonia (OR: 27.65, 95% CI [8.63-88.59]; $p<0.001$), compared to those who received prophylactic antibiotics. For every 50 unit increase in IgA, the odds of reporting pneumonia post-IgRT decreased significantly (OR: 0.82, 95% CI [0.69-0.97], $p=0.018$). Patients with X-Linked Agammaglobulinemia had a lower risk of pneumonia than other PAD diagnoses (OR: 0.84; 95% CI [0.75-0.93]; $p=0.001$). The infectious organism was reported in 39 of 226 patients who reported pneumonia after IgRT. *Haemophilus influenzae* was the most frequently reported ($n=11$, 28.21%), followed by *Streptococcus Pneumoniae* ($n=9$, 23.08%).

Conclusion

Our findings suggest a role for prophylactic antibiotics patients with PAD, especially in those with pre-existing lung disease. However, our study is limited by the cross-sectional nature of the USIDNET database and limited longitudinal data. Therefore, prospective studies evaluating the indications of prophylactic antibiotics are warranted.

Clinical Implications

Patients with primary antibody deficiency and structural lung disease may benefit from prophylactic antibiotics to prevent persisted infections despite IgRT.

Introduction

Primary antibody deficiency disorders (PAD) are humoral immune deficits characterized by defective immunoglobulin production and function, recurrent respiratory, and gastrointestinal tract infections which significantly contribute to morbidity and mortality¹⁻³. 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 infections¹⁰.

Treatment with immunoglobulin replacement therapy (IgRT) via intravenous (IV) or subcutaneous (SC) routes are used to reduce the incidence of infections¹¹. However, a proportion of patients with PAD continue to have persistent respiratory infections¹²⁻¹⁴. 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 to develop 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 United States 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, 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 (HIGM), Hypogammaglobulinemia (unknown cause and no listed genetic defect). We excluded patients if they were not receiving IgRT, or pre/post infections data were unavailable.

Statistical analysis

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

Univariate comparisons were made using 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 ($p < 0.05$)¹⁷.

Odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated for each predictor to examine their contribution to the likelihood of having persistent respiratory infection after initiation of Ig RT. 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, there were N = 1286 patients with a confirmed diagnosis of PAD who were treated with IgRT and had available information on infections post-IgRT. The mean age at PI diagnosis was 22.5 years (0–84). Most patients (82.1%) identified as Caucasian, and 33.7% were female. The most-reported diagnosis was CVID (67.7%). Complete patients' characteristics are summarized in Table 1s. Lung disease (32.7%) was the most commonly reported comorbidity, including asthma (21.5%) and bronchiectasis (7.54%), followed by hematological autoimmune disease and gastrointestinal disease (26.1% and 19.6%, respectively). Out of 1286 included in the study, 339 patients were reported to be receiving prophylactic antibiotics. Patients' comorbidities are further summarized in Table 1s.

Table 1

Patient characteristics

Patients with Pneumonia Post IgG Therapy (n=226)		
Characteristic:		
Gender, n (%)		
Female	87	38.50%
Male	139	61.50%
Age at PI Diagnosis (years)		
All patients, median (range)	12	(0.1-70)
Females, median (range)	28	(0.8-70)
Males, median (range)	6.4	(0.1-63)
Time in Years from Symptom Onset to Diagnosis, median (range)	3	(0-54.1)
PAD Diagnosis, n (%)		
CVID	154	68.14%
Hypogammaglobinemia (including XLA, BTK)	54	23.89%
Specific Antibody Deficiency	7	3.10%
Hyper-IgM (including CD40L)	11	4.87%
Race/ ethnicity, n (%)		
White or Caucasian	167	73.89%
Black or African American	12	5.31%
Asian or Pacific Islander	3	1.33%
Other or more than one race	3	1.33%
American Indian/Native American	1	0.44%
Unknown	40	17.70%
Route of IgRT, n (%)		
Intravenous	129	57.08%
Subcutaneous	57	25.22%
Unknown	39	17.26%
Intramuscular	1	0.44%
Abbreviations: COPD: Chronic Obstructive Lung Disease ITP: Idiopathic Thrombocytopenia Purpura,		

Post-treatment pneumonia and causative pathogens

Pneumonia was reported in 226 patients after the initiation of IgRT (Table 1). Males reported a higher post-IgRT pneumonia frequency compared to females (61.5% vs. 38.5%). Females had a later age of diagnosis in this cohort with a median age of 28 years compared to median age of 6.5 years for males. A PAD diagnosis of CVID (68.1%) was most reported, followed by Hypogammaglobinemia (23.9%) (Table 1). Lung disease was the most common comorbidity (56.2%) (Table 2). Thirty-nine out of 226 patients who reported pneumonia after IgRT also reported the organism of infection that caused their pneumonia. *H. influenzae* was the most frequently reported (n = 11, 28.21%) followed by *S. pneumoniae* (n = 9, 23.08%).

Table 2
Patient comorbidities: Patients with
Pneumonia Post IgG Therapy (n = 226)

Comorbidities, n (%)		
<i>Any respiratory condition</i>		
Asthma	74	32.74%
Bronchiectasis	38	16.81%
COPD	17	7.52%
Interstitial Lung Disease	12	5.31%
Granuloma	8	3.54%
Lung Disease	127	56.19%
Lung Nodules	1	0.44%
<i>Other conditions</i>		
Autoimmune	24	10.62%
Hematological	78	34.51%
ITP	17	7.52%
GI	48	21.24%
Adenopathy	28	12.39%
Celiac Disease	3	1.33%
IBD	18	7.96%
Anemia	41	18.14%
Neutropenia	17	7.52%
Allergies	34	15.04%
Liver	20	8.85%
Spleen	27	11.95%
Abnormal LFTs	6	2.65%
EOE	5	2.21%
Liver Failure	5	2.21%
Pancytopenia	1	0.44%
PLE	3	1.33%

Comorbidities, n (%)		
Thrombocytopenia	19	8.41%

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 3
Immune phenotype: Patients with Pneumonia Post IgG Therapy (n = 226)

Immunoglobulins mg/dL, (range)		
IgA median (range)	9	(0-667)
CVID	15	(0-667)
Hyper-IgM (including CD40L)	6.99	(0-162)
Specific Antibody Deficiency	73	(6-430.8)
Hypogammaglobinemia (including XLA, BTK)	7	(0–97)
IgG median (range)* *IgG levels measures while on IgRT (n = 43)	965	(22-1467)
CVID	972.5	(109–1467)
Hyper-IgM (including CD40L)	1020	1020
Specific Antibody Deficiency	1227.5	(1120–1335)
Hypogammaglobinemia (including XLA, BTK)	145	(22-1270)
IgM median (range)	23.5	(0-648)
CVID	28.5	(0-645)
Hyper-IgM (including CD40L)	117	(20–648)
Specific Antibody Deficiency	58.65	(20–159)
Hypogammaglobinemia (including XLA, BTK)	9	(0-91.6)
Lymphocyte Count (cells/uL), median (range)	1839	(200-10098)
CVID	1700	(200–7958)
Hyper-IgM (including CD40L)	4363	(1670–9000)
Specific Antibody Deficiency	1435.2	(900–6539)
Hypogammaglobinemia (including XLA, BTK)	2800	(700-10098)
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 GLILD; IM, Intramuscular; IV, intravenous; SC, subcutaneous, PAD (Primary Antibody Deficiency		

There was a significant difference in the median IgM value between patients who reported pneumonia post-IgRT and patients who did not [23.5 vs. 29.0, p = 0.021].

There was no significant difference between IgG or IgA, median values between patients who developed pneumonia post IgRT compared to those who did not.

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: Age (18–26 vs. others), IgA (mg/dl—50 unit increments), Absolute Lymphocyte Count (50-unit increments), Bronchiectasis, Interstitial Lung Disease, Autoimmunity, Hematological disease, Asthma, Allergies, Liver Disease, Splenomegaly, COPD, Adenopathy, eosinophilic esophagitis, IgRT therapy type (SCIG or IVIG only), immunosuppressives after beginning IgRT treatment, prophylactic antibiotics, and PID diagnosis (CVID vs. all others & XLA vs. all others).

The backward stepwise selection method was used for the bimodal 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 ($p < 0.05$).

During the process of backward stepwise regression, the following variables were eliminated from the final model due to a p-value of larger than 0.05: Age (18–26 vs. others), Absolute Lymphocyte Count (50-unit increments), autoimmunity, hematological disease, allergies, liver disease, splenomegaly, COPD, Adenopathy, EOE, IgRT therapy type (SCIG or IVIG only), taking immunosuppressives after beginning IgRT treatment, and PID diagnosis (CVID vs. all others).

After performing backward stepwise regression, the final multivariate model included Prophylactic Antibiotic use, XLA (vs. all PID diagnoses), Bronchiectasis, Asthma, Interstitial Lung Disease, and IgA (mg/dl). The area under the ROC curve was 0.7912, indicating that our variable subset is a proper fit for predicting pneumonia after beginning IGRT treatment.

Below are the predicted outcomes for each variable (Table 4):

- Prophylactic Antibiotics
 - Compared to patients who were on prophylactic antibiotics, the patients who were not on prophylaxis had an increase in the odds of reporting pneumonia after IGRT (OR: 27.65, 95% CI [8.63–88.59]; $p < 0.001$), while holding all other variables constant.
- PID Diagnosis

- When comparing all other PID diagnoses to patients who have the diagnosis of XLA, patients with the diagnosis of XLA had a decrease in the odds of reporting pneumonia after IGRT (OR: 0.84; 95% CI [0.75–0.93]; $p = 0.001$), 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 odds of reporting pneumonia after IGRT (OR: 1.79, 95% CI [1.20–2.67], $p = 0.004$), while holding all other variables constant.
- 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: 2.81, 95% CI [1.64–4.80], $p < 0.001$), while holding all other variables constant.
- Interstitial Lung Disease
 - 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: 2.90, 95% CI [1.26–6.70], $p = 0.013$), 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: 0.82, 95% CI [0.69–0.97], $p = 0.018$).

Table 4

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

Determinants	Adjusted OR (95%)	p-value
Prophylactic Antibiotics (no vs yes)	27.65 (8.63–88.59)	< 0.001
XLA (vs all other PID diagnoses)	0.84 (0.75–0.93)	0.001
Comorbidity: ILD	2.90 (1.26–6.70)	0.013
Comorbidity: Asthma	1.79 (1.20–2.67)	0.004
Comorbidity: Bronchiectasis	2.80 (1.64–4.80)	< 0.001
IgA (mg/dl) – 50-unit increments	0.82 (0.69–0.97)	0.018
Area under the curve = 0.7912		
Abbreviations: XLA: X-linked Agammaglobulinemia ILD: Interstitial Lung Disease, OR: Odds ratio, CI: Confidence Interval		

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 immunity¹⁸. 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 immunity²⁴. Additionally, the inability to directly transport IgG to mucosal membranes has been postulated to be a risk factor for persistent infections in patients with PAD¹⁶. Equally important, respiratory viral infections could lead to persistent and severe respiratory infections despite IgRT²⁵.

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}. Comorbidity of XLA and administration of IgA were in contrast protective. In CVID, the presence of bronchiectasis was associated with persistent respiratory infections despite IgRT in those with IgA level < 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 center¹⁴.

We also found that patients on prophylactic antibiotics had a significantly lower risk of developing respiratory infection compared to those who did not receive prophylactic antibiotics. We have previously shown that prophylactic antibiotics are equally effective in preventing infections and hospitalization in specific antibody deficiency compared to immunoglobulin replacement therapy¹¹. Lucas et al. showed a minimal benefit of prophylactic antibiotics¹⁵. However, the study only had 18 patients receiving prophylactic antibiotics for respiratory infections. 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.

Further, we show that having a diagnosis of CVID, or SAD diagnosis, increased persistent pneumonia. CVID accounted for most patients, and most had chronic lung disease. We only included SAD patients receiving IgRT, thus resulting in a selection bias of more severe SAD cases in whom treating physicians identified a need for IGRT (rather than prophylactic antibiotics).

The main strengths of this study include the use of USIDNET registry data; its large size, prospective data collection from thirty-nine institutions, and the broad representation of PAD increases our ability to

generalize results. To our knowledge, 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 of 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, we do not have access to patient charts, dosing of IgRT or its timing, and laboratory data such as IgG trough levels 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. Having chronic lung disease, XLA diagnosis, and low IgA increase the risk of post-IgRT pneumonia, while receiving prophylactic antibiotics decreases the risk of post-IgRT pneumonia.

Our findings suggest a role for prophylactic antibiotics patients with PAD, especially in those with pre-existing lung disease. Our study is limited by the cross-sectional nature of the USIDNET database and limited longitudinal data. Prospective studies evaluating the benefits of prophylactic antibiotics are warranted.

Abbreviations

AID Deficiency activation-induced cytidine deaminase deficiency

aOR Adjusted Odds Ratio

BTK Bruton's tyrosine kinase

CD40L CD40 Ligand

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

Declarations

Ethical 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 to Publish: N/A

Authors Contributions CK and JH performed material preparation, data collection and analysis. The first draft of the manuscript was written by MS and JH. FK, JM and RM contributed critical review and comments on data analysis and manuscript endpoints and overall message. CCR, KS and RF provided significant contributions to the USIDNET database (>10% of patients included). All authors commented on previous versions of the manuscript. All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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Availability of data and materials: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request

Code availability: N/A

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