

Screening for Humoral Immunodeficiency in Patients with Community-Acquired Pneumonia

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BACKGROUND: Immunodeficiency is an underrecognized risk factor for infections, such as community-acquired pneumonia (CAP).

OBJECTIVE: We evaluated patients admitted with CAP for humoral immunodeficiency.

DESIGN: Prospective cohort study

SETTING: Inpatients

PATIENTS, INTERVENTION, AND MEASUREMENTS: We enrolled 100 consecutive patients admitted with a diagnosis of CAP from February 2017 to April 2017. Serum IgG, IgM, IgA, and IgE levels were obtained within the first 24 hours of admission. CURB-65 score and length of hospital stay were calculated. The Wilcoxon rank-sum test, Kruskal-Wallis test, and simple linear regression analysis were used in data analysis.

RESULTS: The prevalence of hypogammaglobinemia in patients with CAP was 38% (95% CI: 28.47% to 48.25%). Twenty-seven of 100 patients had IgG hypogammaglobinemia (median: 598 mg/dL, IQ range: 459-654), 23 of 100 had IgM hypogammaglobinemia

(median: 38 mg/dL, IQ range: 25-43), and 6 of 100 had IgA hypogammaglobinemia (median: 36 mg/dL, IQ range: 18-50). The median hospital length of stay for patients with IgG hypogammaglobinemia was significantly higher when compared to patients with normal IgG levels (five days, IQ range [3-10] vs three days, IQ range [2-5], $P = .0085$). Fourteen patients underwent further immune evaluation, resulting in one diagnosis of multiple myeloma, three patients diagnosed with specific antibody deficiency, and one patient diagnosed with selective IgA deficiency.

CONCLUSION: There is a high prevalence of hypogammaglobinemia in patients hospitalized with CAP, with IgG and IgM being the most commonly affected classes. IgG hypogammaglobinemia was associated with an increased length of hospitalization. Screening immunoglobulin levels in CAP patients may also uncover underlying humoral immunodeficiency or immunoproliferative disorders. *Journal of Hospital Medicine* 2019;14:33-37. Published online first November 28, 2018. © 2019 Society of Hospital Medicine

Community-acquired pneumonia (CAP) is the most common infection in hospitalized patients and the eighth most common cause of death in the United States.¹ Mortality from CAP is estimated to be 5.1% in the outpatient population, 13.6% in hospitalized patients, and 35.1% in patients admitted to the intensive care unit.^{2,3} CAP accounts for more than 50,000 deaths annually in the United States.² There are multiple risk factors for CAP, including tobacco use, malnutrition, chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis, and mechanical bronchial obstruction. Underlying immunodeficiency, specifically humoral immunodeficiency, is also a risk factor for CAP.

Primary immunodeficiency (PID) is estimated to affect one in 1,800 individuals in the United States.⁴ The National Insti-

tutes of Health (NIH) estimates that only one out of three individuals with PID are appropriately diagnosed. Based on probability calculations on known PID patients versus incidence of disease, the NIH estimates that more than 500,000 individuals with PID remain undiagnosed in the United States.⁴ Further, there exists an average diagnostic delay of at least five years. This delay increases both morbidity and mortality and leads to increased healthcare utilization.^{5,6}

The most common form of primary immunodeficiency is due to humoral immunodeficiency, including selective IgA deficiency, specific antibody deficiency, and common variable immunodeficiency. Specific antibody deficiency is defined as a lack of response to polysaccharide antigens in the setting of low to normal Ig levels and an intact response to peptide antigens.⁷ Selective IgA deficiency is defined as the isolated deficiency of serum IgA in the setting of normal serum levels of IgG and IgM in an individual older than four years in whom other causes of hypogammaglobinemia have been excluded.⁸ Common variable immunodeficiency (CVID) is defined as a decreased serum concentration of IgG in combination with low levels of IgA and/or IgM with a poor or absent response to immunization in the absence of other defined immunodeficiency

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state.⁹ In addition to experiencing recurrent infections—namely bronchitis, sinusitis, otitis, and pneumonia—patients with CVID are also at increased risk of autoimmunity and malignancy. In adults, secondary immunodeficiency is more common than primary immunodeficiency. Secondary immunodeficiency occurs commonly with disease states like HIV infection, diabetes, cirrhosis, malnutrition, and autoimmune conditions.¹⁰ Additional causes of secondary immune defects due to humoral immunodeficiency include immune-modulating drugs—such as rituximab and ibrutinib—and hematologic malignancies, including chronic lymphocytic leukemia and multiple myeloma. Recurrent infections remain the leading cause of morbidity and mortality in patients with both primary and secondary immunodeficiency.^{11,12}

Evaluation of the humoral immune system begins with measurement of serum immunoglobulin (Ig) levels. Although abnormal Ig levels are not diagnostic of immunodeficiency, abnormal results may prompt additional evaluation. Screening strategies may assist in making an earlier diagnosis, potentially decreasing morbidity and mortality in patients with immunodeficiency.¹³⁻¹⁵ To date, there have been no studies evaluating the utility of screening Ig levels to evaluate for underlying humoral immunodeficiency in patients hospitalized for CAP.

METHODS

Study Design

This was a prospective cohort study conducted at Rochester General Hospital, a 528-bed tertiary care medical center, from February 2017 to April 2017. We enrolled 100 consecutive patients admitted to the inpatient internal medicine service with a physician diagnosis of CAP. Written consent was obtained from each patient. The study was approved by the institutional review board at Rochester General Hospital.

Case Definition

The following criteria were used to diagnose CAP: (1) Respiratory symptoms of productive cough or pleuritic chest pain, (2) Fever $>38^{\circ}\text{C}$ before or at the time of admission, and (3) chest imaging with infiltrate. Exclusion criteria included a diagnosis of hospital-acquired pneumonia, prior diagnosis of primary immunodeficiency, immunosuppression due to an underlying condition, such as HIV or malignancy, therapy with immunosuppressive medications including chemotherapy, Ig replacement within the past six months, or treatment with >10 mg prednisone for greater than 14 days before hospital admission.

Patients underwent an additional evaluation by a clinical immunologist if they met one of the following criteria: any hypergammaglobinemia (elevated IgG, IgM, or IgA), IgG hypogammaglobinemia <550 mg/dL, undetectable IgM or IgA, or if IgG, IgM, and IgA were all below the lower limit of normal.

CURB-65 was used for estimation of the severity of illness with CAP. The components of the score include age ≥ 65 , confusion, BUN >19 mg/dl, respiratory rate ≥ 30 breaths per minute and systolic blood pressure <90 mm Hg or diastolic blood

pressure ≤ 60 mm Hg. Each component is scored zero if absent or one if present. Predicted mortality ranges from 0.6% for a score of zero to 27.8% for a score of 5.

Data Collection

Patient health information including age, race, gender, medical history, admission notes, results of chest imaging studies, and relevant laboratory studies including serum levels of IgG, IgM, IgA, IgE on admission was obtained from the electronic medical health record. An additional evaluation by the immunologist occurred within three months of hospital discharge and included repeat Ig levels, pre- and postvaccination titers of polysaccharide and peptide antigens, serum protein electrophoresis, and B & T cell panels.

Description of Normal Levels

The normal levels of immunoglobulins were defined based on standard reference ranges at the laboratory at Rochester General Hospital; IgG (700-1,600 mg/dl), IgM (50-300 mg/dl), IgA (70-400 mg/dl), and IgE (0-378 IU/ml). Although there is no established classification regarding the degree of IgG hypogammaglobinemia,¹⁶ clinical immunologists commonly classify the severity of IgG hypogammaglobinemia as follows: mild (550-699 mg/dL), moderate (400-549 mg/dL), and severe (<400 mg/dL) IgG hypogammaglobinemia.

Statistical Analysis

Statistical analysis was performed using STATA software (StataCorp LLC, College Station, Texas). We conducted a Wilcoxon rank-sum test to compare the median difference in length of stay between groups with a low versus normal range of immunoglobulins. A Kruskal-Wallis test was performed to check for the median difference in IgG levels across degrees of illness severity (CURB-65 score categories). We conducted a simple linear regression analysis using the logarithmic data of the length of stay and IgG level variables. A chi-square test was used to determine the association between comorbidities and Ig levels.

RESULTS

Baseline Characteristics

There were 100 patients with CAP enrolled in this study with a median age of 65.04 ± 18.8 , and 53% were female. Forty-seven patients reported a previous history of pneumonia and 18 reported a history of recurrent sinusitis or otitis media. Of the 100 enrolled patients, 46 had received pneumococcal polysaccharide vaccine (PPV23), 26 had received the 13-valent pneumococcal conjugate vaccine (PCV13), and 22 had received both (Table 1). The mean white blood cell count on admission was $12.9 \pm 7 \times 10^3/\mu\text{L}$ with $75 \pm 12.5\%$ neutrophils. Total protein (6.5 ± 0.8) and albumin (3.7 ± 0.5) were within the normal range for the study population.

Immunoglobulin Analyses

The prevalence of hypogammaglobinemia in the study was 38% (95% CI: 28.47% to 48.25%). The median values of Ig levels

for the entire study population and in patients with hypogammaglobinemia are summarized in Table 2.

- *IgG hypogammaglobinemia* (<700 mg/dl) was found in 27/100 patients, with a median level of 598 mg/dL, IQ range: 459-654. The median age in this group was 76.5 years, and 13 were female. Of these 27 patients, 10 had low IgM, four had low IgA, and four had an elevated IgE. In this group, 11 patients had received PPSV23, nine had received PCV13, and six had received both PPV23 and PCV13 before the index hospital admission.
- *IgG hypergammaglobinemia* (>1,600 mg/dl) was found in 9/100 patients, with a median level of 1,381 mg/dL, IQ range: 1,237-1,627. The median age was 61 years, and six were female. Of these nine patients, three had low IgM, one had low IgA, and four had elevated IgE.
- *IgM hypogammaglobinemia* (<50 mg/dl) was found in 23/100 patients with a median level of 38 mg/dL, IQ range: 25-43. In this group, the median age was 69 years, and 10 were female. Of these 23 patients, 10 had low IgG, and three had an elevated IgG.
- *IgM hypergammaglobinemia* (>300 mg/dl) was noted in two patients, with a median level of 491 mg/dL, IQ range: 418-564. Both patients were female, and one had elevated IgG.
- *IgA hypogammaglobinemia* (<70 mg/dl) was discovered in six patients, with a median level of 36 mg/dL, IQ range: 18-50. In this group, four patients had low IgG, four had low IgM, one had elevated IgE, and one had elevated IgG.
- *IgA hypergammaglobinemia* (>400 mg/dl) was noted in five patients, with a median level of 561 mg/dL, IQ range: 442-565: Two patients were female. Of these five patients, one had high IgG, and one had low IgG.

Length of Stay and Severity of Pneumonia

The median length of stay in the hospital for the entire study population was three days (IQ range: 2-5.5 days). Among patients with IgG hypogammaglobinemia, the median length of stay was two days longer as compared with patients who had IgG levels in the normal range (5 days, IQ range [3-10] vs 3days, IQ range [2-5], $P = .0085$).

The median CURB-65 score for the entire study population was two (IQ range: 1-3). The median CURB-65 score did not differ between patients with low and normal ranges of IgG lev-

TABLE 1. Characteristics of Patients

Total participants (n)	100
Age—years	65.04 ± 18.71
Female—no (%)	53 (53%)
Race—no (%)	
White	67 (67%)
African-American	20 (20%)
Hispanic	10 (10%)
Asian	2 (2%)
Indian	1 (1%)
Medical History—no (%)	
COPD	25 (25%)
Asthma	29 (29%)
Bronchiectasis	1 (1%)
Obesity (BMI ≥30)	38 (38%)
Diabetes	27 (27%)
History of physician-diagnosed pneumonia	47 (47%)
History of recurrent sinusitis/otitis	18 (18%)
Current smoker	38 (38%)
Vaccination Status—no (%)	
PPV13 vaccination	26 (26%)
PPV23 vaccination	46 (46%)
History of PPSV 23 + PPV 13 vaccination	22 (22%)
CURB65—no (%)	
0	24 (24%)
1	25 (25%)
2	24 (24%)
3	20 (20%)
4	7 (7%)

Abbreviations: COPD; chronic obstructive pulmonary disease; PPSV; pneumococcal polysaccharide vaccine, PPV, pneumococcal conjugate vaccine.

els (Median: 2, IQ range [1-3] vs Median: 1, IQ range [0-3], $P = .2922$). The CURB-65 score was not correlated with IgG levels ($\rho = -0.0776$, $P = .4428$). Length of stay, however, was positively correlated with CURB-65 score ($\rho = .4673$, $P = .000$).

A simple linear regression analysis using the logarithmic transformation of both length of stay and IgG level revealed a linear relationship between serum IgG levels and hospital length of stay ($P = .0335$, [$R^2 = .0453$]).

TABLE 2. Serum Immunoglobulin Levels in the Study Population

Type	Total Number of Patients	Median (mg/dl)	IQ Range in mg/dl
IgG (700-1,600 mg/dl)	100	941	684.5 -1223
Low IgG (<700 mg/dl)	27	598	459-654
IgA (70-400 mg/dl)	100	228	164-292.5
Low IgA (<70 mg/dl)	6	36	18-50
IgM (50-300 mg/dl)	100	76.5	52-114
Low IgM (<50 mg/dl)	23	38	25-43

TABLE 3. Serum Immunoglobulin Levels in Patients with Diagnosis of Antibody Deficiency

Age in Years	IgG (700-1,600)	IgM (50-300 mg/dl)	IgA (70 -400 mg/dl)	Diagnosis
79	1,904	8	18	Multiple myeloma
77	359	23	30	Selective antibody deficiency
54	680	24	42	Selective antibody deficiency
90	337	79	77	Selective antibody deficiency
56	1,321	100	<18	Selective IgA deficiency

Comorbidities and New Diagnoses

No significant association was found between smoking status, obesity, COPD, asthma, diabetes mellitus, and hypogammaglobulinemia.

Fourteen patients with abnormal Ig levels as defined by (1) the presence of hypergammaglobulinemia (elevated IgG, IgM, or IgA), (2) IgG levels <550, (3) undetectable IgA or IgM, and (4) either IgG or both IgM and IgA below the lower limit of normal underwent further evaluation. Of these 14 patients, one was diagnosed with multiple myeloma, one with selective IgA deficiency, and three with specific antibody deficiency (Table 3).

DISCUSSION

Previous research has evaluated the humoral immune system during an episode of CAP.¹⁷⁻²⁰ Studies on Ig levels in patients with CAP have shown hypogammaglobulinemia to be associated with ICU admission and increased ICU mortality.^{17,20} Additionally, patients with CAP have been shown to have lower IgG₂ levels than healthy controls. The goal of our study was to evaluate patients with CAP for humoral immunodeficiency.

In our study, the prevalence of low Ig levels in CAP was 38%, with IgG hypogammaglobulinemia being the most common class of hypogammaglobulinemia. This rate is slightly higher than that found in a previous work by de la Torri et al.,²¹ who reported a prevalence of 28.9% in the inpatient population. The lower prevalence in the de la Torri et al. study was likely secondary to the exclusion of patients who did not have recorded Ig levels.²¹ Additionally, de la Torri et al. noted an inverse relationship between serum IgG levels and CURB-65. These results were not replicated in our analysis. This is likely due to the relatively low number of patients in each category of CURB-65 score in our study focusing only on inpatients. However, low IgG levels were associated with increased length of stay (5 days, IQ range [3-10] vs 3 days, IQ range [2-5]).

Sepsis can cause hypogammaglobulinemia.^{22,23} The mechanism behind this phenomenon remains unclear, but several theories have been proposed. Sepsis results in endothelial dysfunction, vascular leakage, lymphopenia, and quantitative and qualitative defects in T and B cells.²³ This potentially leads to impaired production and increased catabolism of immunoglobulins. Immunoglobulins play an essential role in recovery from sepsis, and there may be increased consumption during acute illness.²⁴⁻²⁸ Regardless of the mechanism, hypogamma-

globulinemia with SIRS, sepsis, and septic shock has been shown to be a risk factor for increased mortality in these patients.^{22,23} There is currently no consensus on the optimal time to screen for humoral immunodeficiency or evaluate the immune system after infection, such as CAP. Some would argue that Ig levels are lower during an active illness and, therefore, this may not be an appropriate time to evaluate Ig levels. However, we believe that inpatient hospitalization for CAP provides a window of opportunity to selectively screen these patients at higher risk for PID for underlying immune defects. A hospital-based approach as demonstrated in this study may be more productive than relying on an outpatient evaluation, which often may not occur due to patient recall and/or fragmentation of care, thus leading to the well-recognized delay in diagnosis of immunodeficiency.^{5,6}

In our study, one patient was diagnosed with multiple myeloma, three were diagnosed with specific antibody deficiency, and one was diagnosed with selective IgA deficiency. The patient with multiple myeloma was a 79-year old male who presented with his first ever episode of CAP, along with modest anemia and a creatinine of 1.6. His only other infectious history included an episode of sinusitis and one episode of pharyngitis. Additional evaluation included serum and urine electrophoresis, followed by bone marrow biopsy. This patient's multiple myeloma diagnoses may have been missed if Ig levels had not been evaluated. Three patients were diagnosed with specific antibody deficiency. All these patients were above 50 years of age; two out of the three patients in this group had experienced a previous episode of pneumonia, and one had a history of recurrent sinusitis. Lastly, one patient was diagnosed with selective IgA deficiency as defined by undetectable IgA in the setting of normal IgG and IgM. This 56-year-old patient had a history of multiple episodes of sinusitis and three previous episodes of pneumonia, one requiring inpatient hospitalization. Earlier diagnosis of patients with specific antibody deficiency and selective IgA deficiency can guide management, which focuses on appropriate vaccination, the use of prophylactic antibiotics, and the possible role of Ig replacement in patients with specific antibody deficiency.

Of the 100 patients who underwent screening for immunodeficiency in the setting of CAP, five were found to have clinically significant humoral immunodeficiency, resulting in a number needed to screen of 20 to detect a clinically meaningful immunodeficiency in the setting of CAP. The number needed

to screen by colonoscopy to detect one large bowel neoplasm in patients >50 years of age is 23.²⁹ The number needed to screen to diagnose one occult cancer after an unprovoked DVT is 91.³⁰ Based on this information, we feel that future, larger studies are required to evaluate the utility and cost-effectiveness of routine Ig screening for CAP requiring inpatient hospital admission.

We acknowledge limitations to this study. First, this study only evaluated adults in the inpatient floor setting, and therefore the results cannot be applied to the pediatric population or patients in the outpatient or ICU setting. Second, rather than completing a follow-up evaluation in all patients with abnormal immunoglobulins, we selected patients for additional evaluation based on criteria predefined by an immunologist. Although our rationale was to minimize additional diagnostic testing in individuals with mild hypogammaglobulinemia, we acknowledge that this could have led to missing subtler humoral defects, such as a patient with near-normal Ig levels but a suboptimal response to vaccination. Third, due to the design of the study, we did not have a healthy matched control group. Despite these limitations, we believe our results are clinically meaningful and warrant future, larger scale investigation.

In conclusion, there is a high prevalence of hypogammaglobulinemia in patients admitted with the diagnosis of CAP. IgG hypogammaglobulinemia is the most commonly decreased class of Ig, and hospital length of stay is significantly longer in patients with low levels of IgG during admission for CAP. Additional immune evaluation of patients with CAP and abnormal Ig levels may also result in the identification of underlying antibody deficiency or immunoproliferative disorders.

Disclosures: The authors have nothing to disclose

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