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The Clinical Significance of Specific Antibody Deficiency (SAD) Severity in Chronic Rhinosinusitis (CRS)

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Abstract

Background—Despite the increased identification of specific antibody deficiency (SAD) in CRS, little is known about the relationship of SAD severity and the severity and co-morbidities of CRS. The prevalence of an impaired antibody response in the general population is also unknown.

Objective—To determine if the SAD severity stratification applies to real-life data of CRS patients

Methods—An electronic health record database was utilized to identify CRS patients evaluated for humoral immunodeficiency with quantitative immunoglobulins and *Streptococcus pneumoniae* antibody titers pre- and post-pneumococcal vaccine. SAD severity was defined, according to the guidelines, based on the numbers of titers 1.3 µg/dL post-vaccination: severe (2 serotypes), moderate (3–6 serotypes), and mild (7–10 serotypes). Co-morbidities and therapeutic response were assessed. Prevalence of an impaired antibody response in a normal population was assessed.

Results—24% of the CRS patients evaluated for immunodeficiency had SAD while 11% of a normal population had an impaired immune response to polysaccharide vaccination (p<0.05). When evaluated by the practice parameters definition, 239/595 (40%) met the definition of SAD. Twenty-four (10%) had severe SAD, 120 (50%) had moderate SAD, and 95 (40%) had mild SAD.

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Patients with moderate to severe SAD had worse asthma, a greater likelihood of pneumonia, and more antibiotic courses in the two years post-vaccination than patients with mild SAD.

Conclusion—This study provides real world data supporting stratification of SAD by severity, demonstrating a significant increase in the co-morbid severity of asthma and infections in CRS patients with moderate to severe SAD compared to those with mild SAD and those without SAD.

Keywords

Specific antibody deficiency; chronic rhinosinusitis; immune deficiency

Introduction

Chronic rhinosinusitis (CRS) is a heterogeneous disorder characterized by local inflammation of the paranasal sinuses which persists for greater than 12 weeks. CRS affects approximately 12.5% of the United States' population, approximately 31 million people¹. CRS incurs a significant economic burden on the health care system and society. CRS is divided into two main subtypes: CRS with nasal polyps (CRSwNP) which accounts for up to one third of cases and CRS without nasal polyps (CRSSNP) which accounts for the remaining two-thirds of patients². CRS is one of the most common manifestations of humoral immunodeficiency.

Humoral immunodeficiencies range from severe to mild depending on the quantity of antibody production and function. Common variable immune deficiency (CVID) is the most common symptomatic antibody deficiency associated with both decreased antibody production and function as evident by poor responses to both polysaccharide and protein antigen vaccines. Specific antibody deficiency (SAD) is a primary immune deficiency associated with a qualitative defect in antibody function. SAD is defined as an inability to make specific antibodies in response to polysaccharide antigens, such as Pneumovax®, in the presence of recurrent or chronic sinopulmonary infections. It is characterized by normal immunoglobulin levels and normal cellular immunity. A recent meta-analysis by Schwitzguebel et al has shed light on the high prevalence of humoral immune deficiency in CRS with 12.3% of subjects with recurrent CRS diagnosed with CVID, IgA deficiency, IgM deficiency, or an unspecified IgG deficiency and 8–34% diagnosed with SAD³.

In September 2012, the Working Group of the Basic and Clinical Immunology section of the American Academy of Allergy, Asthma, and Immunology published guidelines regarding the use of vaccinations and the diagnosis of SAD in the assessment of primary immune deficiencies⁴. This report stratified SAD into 4 subtypes based on the degree of non-responsiveness to a polysaccharide vaccine: severe, moderate, mild, and memory. The most recent practice parameter on primary immunodeficiencies highlights this stratification of SAD severity as well⁵. The practice parameter is among the most commonly used guidelines for the management of patients with immunodeficiencies; yet, the current interpretation of vaccine response through measurement of antibody titers is based on expert consensus opinion. The objective of this study to assess if the severity stratification of SAD as described in the Working Group report and recent practice parameter on primary immunodeficiencies applies to real-life data of patients with CRS. To the best of our knowledge, this is the first report characterizing patients with CRS based on SAD severity

subtypes. In addition, research and interpretation of vaccine response has been hampered by the lack of data for post vaccine response in otherwise healthy individuals. This study also reports the prevalence of an impaired antibody response to a polysaccharide vaccine in healthy individuals, which has previously not been well studied.

Methods

A retrospective electronic database chart review, approved by the Institutional Review Board of Northwestern University Feinberg School of Medicine, was undertaken to evaluate the prevalence and clinical characteristics of adult patients at a tertiary allergy-immunology and otolaryngology clinic in Chicago, IL. Electronic health record data from the Northwestern Medicine Enterprise Data Warehouse was utilized to identify patients with CRS based on the International Classification of Disease, Ninth Revision (ICD-9) who were evaluated for humoral immunodeficiency with quantitative immunoglobulins and *Streptococcus pneumoniae* antibody titers. 2518 patients were identified by the Northwestern Medicine Enterprise Data Warehouse. Subjects met inclusion criteria if they had a visit at the allergy-immunology or otolaryngology clinic at the university between January 1, 2010 and February 28, 2013, met the criteria for CRS as defined by nationally recognized consensus statements⁶, had a sinus computed tomography (CT) scan documenting CRS, and had *Streptococcus pneumoniae* antibody titers pre- and post-pneumococcal polysaccharide vaccine. The treating physician made the decision to evaluate the individual patient with CRS for immunodeficiency. Subjects were excluded from the study if they had allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, primary ciliary dyskinesia, cystic fibrosis, hematologic malignancy, or acquired immunodeficiencies (e.g. HIV/AIDS or secondary to medications such as chemotherapy). 595 patients met the inclusion and exclusion criteria and were eligible for the study. Raw data from subjects with CRS without SAD was obtained from Kashani et al and represents subjects from 2002 to 2009 with the same inclusion and exclusion criteria as above⁷.

Evaluation of humoral immune status

A patient's humoral immune status was classified on the basis of their quantitative immunoglobulin levels (IgG, IgA, and IgM) and the number of adequate pneumococcal antibody titers post Pneumovax® as described in the practice parameter⁵. Serum IgG antibody titers to 14 common pneumococcal serotypes (1, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 12F, 14, 18C, 19F, 23F) were measured for each subject by the pneumococcal immunity assay on the Luminex® system (Specialty Laboratories Inc., Valencia, CA). Adequate antibody levels were defined as protective titers (≥ 1.3 ug/mL)^{4,5}. The diagnosis of CVID was made based on an IgG level less than two standard deviations below the mean of a standard reference population and a low IgA and/or low IgM with an inadequate response to polysaccharide vaccination⁵. The diagnosis of IgA deficiency was made in patients with undetectable IgA levels⁵.

Regarding SAD evaluation and diagnosis, subjects with adequate pre-immunization titers (≥ 1.3 μ g/mL in 7 or more of 14 pneumococcal serotypes) were categorized as "normal baseline". Subjects with low pre-immunization titers (<7 out of 14 pre-immunization titers

1.3 µg/mL) were categorized as “low baseline,” immunized with Pneumovax® (23-valent unconjugated pneumococcal polysaccharide vaccine, Merck), and had titers checked 4–6 weeks after immunization. Subjects with an adequate response to the vaccine, defined as post-immunization titers ≥ 1.3 µg/mL for at least 7 of fourteen serotypes, were categorized as responders. Patients with a “normal baseline” or responders to vaccination were considered to have normal immune function.

At our institution, subjects with post-immunization titers < 1.3 µg/mL for fewer than 7 of fourteen serotypes, were categorized as nonresponders and diagnosed with SAD. This varies from the most recent practice parameter and the Working Group report which define SAD as fewer than 70% protective titers post pneumococcal vaccine and then further stratified SAD as mild, moderate or severe subtype based on numbers of protective titers. For the purposes of characterizing the subjects based on the Working Group severity subtypes, we followed their guidelines.

Evaluation of subjects' clinical characteristics

Lund-Mackay score assessments were performed on pre-surgery CT scans or the most recent scan if the patient had no history of sinus surgery^{8,9}. Lund-Mackay scores range from 0 to 24 with higher scores being indicative of greater CRS severity. In accordance with the Task Force on Rhinosinusitis recommendations, only scans with a Lund-Mackay score of greater than 4 were included in the analysis^{10,11}. The presence of nasal polyposis was determined by rhinoscopy or sinus CT scan; subjects were classified as CRSwNP or CRSsNP based on this evaluation. Allergic rhinitis was determined in all subjects via positive skin testing to grass, tree, ragweed, dust mite, mold, cat, dog, and cockroach (Hollister-Stier extracts, Spokane, WA) and presence of rhinitis symptoms. Asthma diagnosis and severity was determined in accordance with the 2007 NAEPP Expert Panel Report 3 guidelines using %FEV1 values¹². Diagnosis of lower airway abnormalities such as bronchiectasis, nodules, and ground glass opacities, on a chest CT scan, with high resolution when applicable, were made by the attending radiologists who read the films. History of pneumonia, antibiotic use, and immunoglobulin (Ig) treatment was determined by extensive chart review including clinic visit and telephone encounter documentation, medication reconciliation forms, and review of radiology.

Analysis of impaired antibody response to vaccination in a normal population

98 healthy adult individuals (ages 18–92) without a history of recurrent infections had previously been recruited¹³. Serum IgG antibody titers to 14 common pneumococcal serotypes were measured for each subject by the pneumococcal immunity assay on the Luminex® system pre- and post-pneumococcal vaccination with Pneumovax®. These subjects were analyzed for impaired antibody response to vaccination. Subjects with post-immunization titers < 1.3 µg/mL for fewer than 7 of fourteen serotypes, were categorized as having an impaired antibody response to vaccination.

Statistical analysis

Evaluation of subjects' characteristics, anti-pneumococcal antibody titers, and serum immunoglobulin levels was performed via ANOVA with post-hoc Tukey analysis.

Analogous Chi-square tests were used to compare percentages for categorical variables. Data are expressed as mean with standard deviation. A p-value less than 0.05 was considered statistically significant. Statistical analysis was performed using Stata version 10.

Results

Prevalence of Immune Deficiency in CRS

Of the 595 patients with CRS evaluated for humoral immunodeficiency, SAD (defined as <7/14 (50%) serotypes 1.3 µg/mL) was the most prevalent immune deficiency with 144 (24.2%) of patients diagnosed with SAD. When these patients were categorized according to the Working Group and practice parameter's definition of SAD, 239 of the 595 (40.2%) of the patients met the criteria for SAD. Thirty-five patients (5.9%) had CVID and nine patients (1.5%) had IgA deficiency (Figure 1A).

Prevalence of Impaired antibody response in a Normal Population

In a study of 98 healthy adult individuals (ages 18–92) without a history of recurrent infections¹³, 11.2% (11 individuals) were diagnosed as having an impaired immune response to a polysaccharide vaccination (<50% protective post-immunization titers). There was a statistically significant difference between the prevalence of SAD in patients with CRS (24.2%) and the prevalence of impaired antibody response in a normal population (11.2%) ($p < 0.05$) (Figure 2). When using the Working Group and practice parameters definition of 70% protective titers, 20 of these healthy individuals (20.4%) would be diagnosed with an impaired antibody response compared to the 40.2% prevalence of SAD in patients with CRS with this definition. Instituting the severity stratification for SAD on these individuals, 9 of the 20 would be classified as mild (45%), 8 as moderate (40%), and 3 as severe (15%).

Characteristics of CRS patients with SAD as defined by the Working Group

Clinical characteristics of the 239 subjects who met the Working Group report and practice parameter's definition of SAD (less than 70% protective anti-pneumococcal titers post polysaccharide vaccine) are presented in Table 1. As shown in figure 1B, 24 (10.0%) had 2 or fewer protective titers and were classified as severe SAD. One hundred twenty (50.2%) had less than 50% protective titers, or 3–6 protective titers, and were classified as moderate SAD severity. Ninety-five (39.8%) had between 50–70% protective titers and were classified as mild. Patients with mild SAD were more likely to be younger than patients with moderate or severe SAD. There was no difference in gender or race between the three groups. Patients with mild SAD were more likely to have higher IgG levels than those with severe SAD, and there was no difference in IgA or IgM levels between the three classes of SAD severity. Patients with moderate SAD severity were more likely to have asthma compared to those with severe or mild SAD severity. There was no significant difference in the presence of allergic rhinitis, nasal polyps, or a history of sinus surgery between the three SAD severity groups.

Radiographic severity of CRS as stratified by SAD severity

The Lund-Mackay scoring system was used to assess radiographic severity of CRS by measuring opacification of the sinuses and ostiomeatal complexes. In this cohort, the severity of SAD did not predict the severity of sinus disease radiographically. Patients with mild or moderate severity of SAD had higher Lund-Mackay scores than those patients with severe SAD. The mean Lund-Mackay score was 9.15 for the mild SAD severity group, 9.96 for the moderate group, and 5.50 for the severe SAD group. The association was consistent even when controlled for the presence of nasal polyps.

Presence of comorbid asthma and radiographic lung abnormalities in patients with CRS as analyzed by SAD severity

Electronic medical records of patients were surveyed for the presence of physician-diagnosed asthma and radiographic lung abnormalities. CRS subjects with moderate SAD severity were more likely to have asthma compared to those with severe or mild SAD severity. The 136 CRS patients with asthma were assessed for asthma severity¹². Patients with a diagnosis of moderate or severe SAD, the group with less than 50% protective titers, were more likely to have moderate to severe asthma by these guidelines, compared with those patients with mild SAD (50–70% protective titers). There was a trend toward a lower FEV1 in the moderate to severe SAD group (FEV1 81% predicted) compared to the mild SAD group (FEV1 88% predicted) although this did not reach statistical significance. There was no significant difference in the presence of radiographic evidence of lung disease between the three SAD severity groups.

Infection history of CRS patients as stratified by SAD severity

The cohort of CRS subjects with SAD was assessed for a history of pneumonia. As shown in Figure 3, patients with moderate and severe SAD, or the subjects with less than 50% protective titers, were more likely to have a history of pneumonia, compared with those patients with mild SAD who had 50–70% protective titers. The number of antibiotic courses that CRS subjects received in the 2 years post-vaccination were surveyed and analyzed. The severe and moderate SAD severity groups had a statistically significant greater number of antibiotic courses in the 2 years post Pneumovax®, 5.38 and 3.82 respectively, than the subjects in the mild SAD severity group who had a mean of 2.35 antibiotic courses in the 2 year period (Figure 4). Data previously published from our institution demonstrated that CRS controls without SAD also had a mean of 2.19 antibiotic courses in the 2 year period post-vaccination, similar to the mild SAD group⁷.

Immunoglobulin replacement therapy in CRS subjects with SAD

In the cohort of 144 CRS subjects with moderate to severe SAD, 24 (21%) were on immunoglobulin replacement therapy. There was no difference in Ig replacement use between the moderate and severe SAD groups. Subjects with > 50% protective antibody titers (the mild SAD group) were not included in this analysis as they were not classified as having an immune deficiency in our institution and therefore, not considered for Ig replacement by the treating physicians. CRS patients with SAD and a history of pneumonia

were more likely to be on Ig replacement than those patients without a history pneumonia, regardless of SAD severity ($p<0.05$).

Discussion

The evaluation of humoral immunodeficiency is undertaken in many patients with CRS to aid in determining an underlying etiology of their sinonasal inflammation and recurrent infections. Specific antibody deficiency is found in nearly one-quarter of CRS patient with recurrent sinus infections. This study confirms the prevalence of SAD in CRS as previously published by our group⁷. The cohort in Kashani et al assessed the prevalence of SAD in subjects with CRS from 2002–2009 and the current study addresses the prevalence of SAD in CRS subjects from 2010–2013. The prevalence of SAD in this CRS cohort has not been increasing even with greater surveillance for the disease.

The diagnosis of SAD in patients with CRS has been controversial as the antibody response in a control population was previously not well defined. This study addresses the prevalence of an impaired antibody response in a normal, healthy population. 11.2% of the control population without recurrent infections was diagnosed with an impaired response to a polysaccharide vaccination. The prevalence of SAD in the CRS cohort was significantly higher than the prevalence of an impaired antibody response in the normal population and suggests that impaired immunity may be a factor in the development of CRS.

In addition, what constitutes an adequate number of protective serotypes post pneumococcal vaccine is controversial and is based on expert opinion. This study defines SAD as less than 50% protective serotypes after a polysaccharide vaccine to minimize over diagnosis of immunodeficiency. We also classified the patients based on the Working Group and practice parameter's categorization of SAD subtypes to assess the characteristics of CRS patients based on severity. The classification of SAD severity published by the Working Group stratifies SAD severity by number of protective antibody titers. The severity classification structure does not take into account clinical characteristics such as number or severity of infections. Therefore, this study seeks to assess the validity of this classification structure in real world data of patients with CRS. Patients with moderate to severe SAD were more likely to have more severe asthma, a history of pneumonia, and require a greater number of antibiotic courses in the 2 years post-vaccination than patients with mild SAD. While SAD severity did not correlate with radiographic severity of CRS by Lund-Mackay score, this may have been driven by a low number of severe SAD patients with available CT sinus scans. Lund-Mackay scores have been reported to correlate well with the extent of sinus surgery required and surgical outcomes; however, these scores have not been found to correlate with disease severity markers by patient symptom scores, including SNOT-22, and subjective changes in disease severity^{9,14}. Therefore, Lund-Mackay scores may not be the optimal measure for assessing disease severity in CRS^{9,15,16,17}.

In comparing clinical characteristics between patients with moderate to severe SAD (those with <50% protective titers) and patients with mild SAD (those who mount a 50–70% protective titer response), the frequency of sinopulmonary infections in patients with mild SAD was significantly lower than those patients who mounted a protective response to less

than 50% of serotypes. The mild SAD group had a higher prevalence of pneumonia than the CRS controls without SAD but it was significantly less than the moderate to severe SAD patients. Both patients with mild SAD and CRS controls without SAD required a similar number of antibiotic courses in the 2 years studied. Therefore, the mild SAD group, in some ways, resembled a normal population and it may not represent as significant a state of functional antibody deficiency as the moderate to severe SAD population who mounted a protective response to fewer than 50% of serotypes. Based on these findings, the current SAD severity classification by the Working Group and practice parameter appears to be accurate in a real world setting of CRS patients; still, the clinical relevance of mild SAD must be explored through further research to determine if these patients truly have a predisposition to increased infections like the moderate and severe SAD groups. This is necessary because labeling the mild SAD group with an immunodeficiency may lead to unnecessary stress for patients, particularly those without severe infections. Due to the diagnosis of immunodeficiency, these mild SAD patients may be more likely to receive antibiotics inappropriately for non-bacterial infections. Smith et al demonstrated that rhinosinusitis was the leading cause of outpatient antibiotic prescriptions¹⁸. Given increasing bacterial resistance and the potential for adverse drug reactions, the need for judicious antibiotic use, which extends to the therapeutic and prophylactic use in immune deficiencies, is critical. It may be prudent to clinically monitor patients who fall into the mild SAD group individually for recurrent bacterial infections as the guide for initiating prophylactic antibiotics or immunoglobulin replacement as once these therapeutic strategies are initiated, they often result in life long therapy even if there is no significant perceivable benefit.

There was no difference in immunoglobulin replacement use as stratified by SAD severity in our patient population but those patients with a history of pneumonia were more likely to require Ig replacement therapy. It is important to note that only those with moderate and severe SAD severity received Ig replacement and no one in the mild group received Ig therapy. Our findings suggest that presence of comorbid history of pneumonia may be important when considering Ig replacement for patients with SAD and CRS.

Immunoglobulin replacement has demonstrated efficacy in preventing serious, invasive bacterial infections in humoral immune deficiencies; however, the benefit in CRS and recurrent sinus infections is unclear¹⁹. A classification system for SAD, similar to one previously developed for CVID²⁰, which incorporates both laboratory analysis and clinical characteristics such as a history of pneumonia may be useful in stratifying patients for use in algorithms to guide treatment with Ig replacement.

This study has demonstrated clinical characteristics of a large population of patients with SAD and CRS. It is consistent with previously published data and includes novel findings regarding the prevalence of impaired antibody production in a normal population and the application of the Working Group classification and practice parameter to a real world setting. This study sets the framework for further classification schemes for SAD which include both clinical and laboratory-based characteristics. This study has several methodological limitations. It is a retrospective, observational cohort of adult patients at a tertiary medical center so the results may not be generalizable to all patient groups, particularly children. The patients were treated by multiple physicians in the practice and there were no uniform criteria for antibiotic use for infections or Ig replacement. Every

effort was made to collect all antibiotic data by extensive chart review; still, it is possible that antibiotics prescribed at other institutions may have been missed. Additionally, not all patients had chest radiography available for review and this limited the number for analysis. Subjects in the normal, healthy control population were adults evaluated by Borgers et al in Belgium and may not be fully generalizable to the population in the United States¹³. Exposure to *Streptococcus pneumoniae* and pneumococcal vaccination recommendations are similar in both Belgium and the United States²¹; however, this control group did not include subjects aged 31–57 years old which may limit comparisons to the CRS population in this age range. Additionally, selection bias may limit the comparison of SAD prevalence between the CRS group and prevalence of impaired antibody production in the normal group as treating physicians decided which CRS patients to evaluate for immune deficiency based on clinical characteristics. Future prospective studies regarding treatment options, including the utility of immunoglobulin replacement, as stratified by SAD severity, should be undertaken.

In conclusion, consider screening for immune deficiency in patients with CRS but it may be prudent to limit screening for SAD to patients with severe CRS, who require more frequent antibiotic courses and those with evidence of a lower airway abnormality such as asthma or a history of pneumonia. This may decrease financial costs associated with screening for immunodeficiencies as well as limit over diagnosis and unnecessary treatment including antibiotic use. Patients with 50–70% protective titers, the mild SAD group, may be over-diagnosed as having an antibody deficiency, as their clinical characteristics are not fully consistent with the patients who mount a protective response to less than 50% of serotypes. Further research is necessary to determine if patients in the mild SAD group have a greater predisposition to infections than normal controls. A classification scheme for specific antibody deficiency severity which incorporates both clinical and laboratory characteristics may be useful to guide treatment algorithms in the future.

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Abbreviations

CRS	chronic rhinosinusitis
CRSsNP	chronic rhinosinusitis without nasal polyps
CRSwNP	chronic rhinosinusitis with nasal polyps
CVID	common variable immune deficiency
CT	computed tomography
FEV1	forced expiratory volume in the first second of expiration
ICD-9	International Classification of Disease Ninth Revision
Ig	Immunoglobulin

NAEPP National Asthma Education and Prevention Program

SAD specific antibody deficiency

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Highlights

1. What is already known about this topic?

Chronic rhinosinusitis (CRS) is a common manifestation of humoral immunodeficiency, particularly specific antibody deficiency (SAD). A Working Group report and recent practice parameters stratified SAD by severity of antibody deficiency; however, this stratification requires validation in a real world setting.

2. What does this article add to our knowledge?

CRS patients with more severe SAD were more likely to have evidence of lower airway abnormalities and require frequent antibiotic courses. This study reports the prevalence of an impaired antibody response to a polysaccharide vaccine in a normal population.

3. How does this study impact current management guidelines?

Consider screening for immune deficiency in patients with CRS, particularly those with a history of pneumonia, asthma or who require more frequent antibiotic courses. Patients with severe SAD may require more monitoring and treatment than those with mild SAD.

Figure 1A

Figure 1B

Figure 1.

Figure 1A: Prevalence of immune deficiency in chronic rhinosinusitis (n=595, using a 50% cutoff for protective antibody titers in SAD). CVID, Common variable immune deficiency; SAD, specific antibody deficiency. The normal group contains patients with a normal baseline and responders to vaccination with adequate titers post-Pneumovax®.

Figure 1B: Prevalence of SAD severity phenotypes in CRS according to the Working Group classification (n=239, using a 70% cut-off for protective antibody titers). CRS, chronic rhinosinusitis; SAD, specific antibody deficiency.

Figure 2. Comparison of percentage of patients with impaired antibody response in normal controls vs. CRS patients evaluated for immunodeficiency. CRS, chronic rhinosinusitis.

Figure 3. History of pneumonia reported in the medical record as stratified by SAD severity. SAD, specific antibody deficiency

Figure 4. Antibiotic use in the 2 years post-Pneumovax® vaccination as classified by SAD severity. SAD, specific antibody deficiency.

Table 1

Subject characteristics

	Severe (n=24)	Moderate (n=120)	Mild (n=95)	Total SAD (n=239)	p-value
Age, years	51.3	51.4	44.8	48.8	0.00*
Male (%)	4 (16.7)	39 (32.5)	26 (27.4)	69 (28.9)	0.27
Caucasian (%)	20 (83.3)	85 (70.8)	60 (63.2)	165 (69.0)	0.19
African American (%)	3 (12.5)	10 (8.3)	11 (11.6)	24 (10.0)	0.67
Immunoglobulin Levels					
IgG (mg/dl)	840	951	1024	969	0.01*
IgA (mg/dl)	171	199	195	195	0.47
IgM (mg/dl)	98	108	118	111	0.42
Asthma (%)	11 (45.8)	80 (66.7)	49 (51.6)	140 (58.6)	0.03*
Allergic rhinitis (%)	15 (62.5)	78 (65)	70 (73.7)	163 (68.2)	0.33
Nasal polyps (%)	2 (8.3)	31 (25.8)	20 (21.1)	53 (22.2)	0.16
Sinus surgery (%)	12 (50.0)	71 (59.2)	49 (51.6)	132(55.2)	0.47