

Comparison of management options for specific antibody deficiency

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ABSTRACT

Background: Specific antibody deficiency is a primary immunodeficiency characterized by normal immunoglobulins with an inadequate response to polysaccharide antigen vaccination. This disease can result in recurrent infections, the most common being sinopulmonary infections. Treatment options include clinical observation, prophylactic antibiotic therapy, and immunoglobulin supplementation therapy, each with limited clinical data about their efficacy.

Objective: This study aimed to identify whether there was a statistically significant difference in the rate of infections for patients who were managed with clinical observation, prophylactic antibiotics, or immunoglobulin supplementation therapy.

Methods: A retrospective chart review was conducted. Patients were eligible for the study if they had normal immunoglobulin levels, an inadequate antibody response to polysaccharide antigen-based vaccination, and no other known causes of immunodeficiency.

Results: A total of 26 patients with specific antibody deficiency were identified. Eleven patients were managed with immunoglobulin supplementation, ten with clinical observation, and five with prophylactic antibiotic therapy. The frequency of antibiotic prescriptions was assessed for the first year after intervention. A statistically significant rate of decreased antibiotic prescriptions after intervention was found for patients treated with immunoglobulin supplementation ($n = 11$; $p = 0.0004$) and for patients on prophylactic antibiotics ($n = 5$; $p = 0.01$). There was no statistical difference in antibiotic prescriptions for those patients treated with immunoglobulin supplementation versus prophylactic antibiotics ($p = 0.21$).

Conclusion: Prophylactic antibiotics seemed to be equally effective as immunoglobulin supplementation therapy for the treatment of specific antibody deficiency. Further studies are needed in this area.

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Specific antibody deficiency (SAD) is a primary humoral immunodeficiency characterized by normal levels of immunoglobulins with an inadequate response to polysaccharide antigen vaccination.¹ It is diagnosed in patients ages > 2 years. In addition, it is one of the most common immunodeficiencies.² Because SAD is primarily a humoral immunodeficiency, assessment of B-cell function is crucial for a diagnosis. Polysaccharide-based vaccinations are used as an assessment of B-cell function. Protein-based or conjugate vaccinations primarily evaluate T-helper cell function. As a result, patients with the diagnosis of SAD typically have a normal response to protein antigen vaccinations or conjugated vaccinations. The spectrum of SAD can range from mild to moderate

to severe, depending on the severity of impairment of the antibody response. Sinopulmonary infections are a frequent complication of this disease;^{3,4} however, the spectrum of infections for this disorder is quite variable. As an example, SAD has been diagnosed in patients with bronchiectasis of unknown etiology⁵ but may also manifest as recurrent otitis infections that are difficult to treat with antibiotics or that require tympanostomy tubes.

Only a few purely polysaccharide antigen-based vaccines are commercially available. They currently include a *Salmonella* Typhi polysaccharide vaccine and a 23-valent pneumococcal polysaccharide antigen vaccine. The 23-valent vaccination contains antigens to the organism *Streptococcus pneumoniae*. Conjugated vaccines, such as the 13-valent pneumococcal polysaccharide vaccine, contain polysaccharide antigens that are conjugated to proteins to induce better antibody responses to the polysaccharide antigens. The ability to mount a response to vaccinations that contain polysaccharide antigens is dependent on the age of the individual as well as the serotype being assessed.⁶ Because children are increasingly being vaccinated with the 13-valent pneumococcal polysaccharide antigen vaccination, the interpretation of the pneumococcal antibody serotypes may be difficult. A serotype level of 0.35 $\mu\text{g/mL}$ has been proposed to be protective for the 13-valent pneumococcal vaccination.⁷

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Currently, the laboratory used to assess the response to this vaccination has serotypes that overlap with the 13-valent conjugated vaccination and the 23-valent polysaccharide antigen vaccination. The most common method of diagnosing SAD is to assess antibody levels to 23 pneumococcal serotypes by vaccinating with 23-valent pneumococcal polysaccharide antigen vaccination, and, subsequently, checking antibody serotype between 4 and 6 weeks after vaccination.⁶ These serotypes can be assessed by a Luminex-based direct immunoassay, enzyme-linked immunosorbent assay method, or the global test. The values are expressed as $\mu\text{g/mL}$. The global test evaluates antibody response by using the 23 different serotypes as a single antigen. Although the global test is inexpensive, the reproducibility of this test is questionable.³

However, the definition of “inadequate response” to polysaccharide vaccination is controversial. A serotype of $>1.3 \mu\text{g/mL}$ is considered effective at protecting against serious infections from *S. pneumoniae*.³ A normal response to a pneumococcal vaccine is considered as $>50\%$ of serotypes having a serotype level of $>1.3 \mu\text{g/mL}$ for children <6 years of age and as $>70\%$ in patients ages ≥ 6 years.² Yet, this definition is based largely on expert opinion as opposed to clinical studies.⁷ Additional studies demonstrated that a polysaccharide response of $>50\%$ serotype levels $>1.3 \mu\text{g/mL}$ even in the adult population could be considered a normal response^{8,9}; however, the definition of SAD has not changed based in any recent literature.

Because no best-practice guidelines exist for treating patients with SAD, current management strategies for this disease are based on expert opinion and not on clinical studies.¹⁰ Treatment options include clinical observation, prophylactic antibiotics, and initiation of immunoglobulin supplementation, all of which have inherent risks. Prophylactic antibiotics can risk

increasing infections with antibiotic-resistant organisms.¹¹ In addition, antibiotics may have adverse effects, such as gastrointestinal complications. Intravenous immunoglobulin supplementation risks thromboembolic disease, aseptic meningitis, and nephrotoxicity. Although these risks may be less with subcutaneous immunoglobulin supplementation, they are not absent. The aim of this study was to determine whether patients diagnosed with SAD who were managed with immunoglobulin supplementation, prophylactic antibiotics, or clinical observation showed a statistically significant difference in frequency of infections.

METHODS

Approval for this study was obtained through the institutional review board at the University of Kansas Medical Center. This study was a retrospective review conducted with an electronic data base called Heron at a tertiary medical center in Kansas City, Kansas. In the Heron data base, the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* and *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* codes that correspond best with SAD were searched. These included the codes *ICD-9-CM* 279.00–279.90 and *ICD-10-CM* D80–89. The search criteria were entered into the Heron data base with no additional modifiers. The search revealed 146 patients with these diagnosis codes, all of whom had been seen after the 2011 acquisition of electronic medical records at the tertiary medical center. Each chart was then individually reviewed for patient age, sex, immunoglobulin levels, preimmunization serotypes for 23-valent pneumococcal polysaccharide antigen vaccination, and postimmunization serotypes (Table 1). Absolute levels of B cells, T cells, and natural killer cells were noted. The

Table 1 Characteristics of the patients in each treatment arm

Parameters	Reference Ranges	Treatment Arm		
		Clinical Observation (n = 10)	Prophylactic Antibiotics (n = 5)	Immunoglobulin Therapy (n = 11)
Mean age, y		57	66	55
Mean baseline IgG level,	762–1488	918	882	910
Mean baseline IgA level,	70–390	178	148	203
Mean baseline IgM level,	38–328	54	71	92
Mean postvaccination percentage of pneumococcal serotypes $1.3 \mu\text{g/mL}$	>70	32.5	41	39

IgG = Immunoglobulin G.

antibody titer level to tetanus toxoid was also noted. A review of this information allowed confirmation of a SAD diagnosis for the included patients. In addition, information was obtained and recorded on atopic disease, treatment of atopic disease, chronic obstructive pulmonary disease status, heart disease status, kidney disease status, diabetes mellitus status, immunosuppression, and cancer status. In addition, it was noted whether the patient was currently alive or deceased. Patients were excluded if they were under the ages of <18 years, were on immunosuppressive agents, or did not meet the criteria for SAD.

An adequate response to 23-valent pneumococcal polysaccharide antigen vaccination was determined by pre- and postimmunization serotype levels. Nonresponders were determined to have a postvaccination serotype level of <1.3 µg/mL of <70% of the 23 serotypes. The charts were individually reviewed to determine each infection documented by the primary immunologist. The number and type of infections that the patient was having per year before a SAD diagnosis were documented. Subsequently, the number and type of infections that the patient experienced after his or her management plan was determined were also recorded. A total of 31 patients were found to meet the diagnosis of SAD and were followed up in the medical center's allergy and immunology clinic. Data on the rate of antibiotic prescriptions were missing from five charts. Ultimately, 26 patients were included in this study. The rate of antibiotic prescription was determined by reading providers' notes and viewing antibiotic prescriptions. Data before 2011 were not available in the electronic medical records. The type of immunoglobulin supplementation was noted (intravenous or subcutaneous). The type of antibiotic used for both prophylaxis and treatment was also noted. The antibiotic prescriptions for prophylaxis were excluded from the count of antibiotic prescriptions per patient.

The mean number of infections per year was determined both before and after the intervention. The definition of infection and determination of antibiotic need was determined by the individual immunology provider. A paired *t*-test analysis was used to determine if the

rate of antibiotic prescriptions significantly decreased with immunoglobulin supplementation or prophylactic antibiotics compared with clinical observation. With the use of the general linear model, an analysis of covariance was used to determine if the rate of antibiotic prescriptions was significantly different when comparing the immunoglobulin supplementation arm to the prophylactic antibiotic arm. In addition, a folded *F* test was done to check the equality of the variances.

RESULTS

Of the 26 patients, 10 were in the clinical observation arm, 11 were in the immunoglobulin supplementation arm, and 5 were on prophylactic antibiotics. In the clinical observation arm, 3 of the 10 patients had a severe SAD phenotype. In the immunoglobulin supplementation and prophylactic antibiotic arms, all the patients had a moderate SAD phenotype (*n* = 16). The rate of antibiotic prescriptions was assessed for the first year after the intervention. Of the patients in the immunoglobulin supplementation arm, 45% had five or more antibiotic prescriptions per year (*n* = 5). Of the patients in the prophylactic antibiotic arm, 20% had five or more antibiotic prescriptions per year (*n* = 1). Also, of the patients in the clinical observation arm, 27% had five or more antibiotic prescriptions per year (*n* = 3).

The prophylactic antibiotics used included either azithromycin 250 mg on Mondays, Wednesdays, and Fridays, or doxycycline, 100 mg daily. The mean immunoglobulin G level for all the patients in the study was 908. The mean percentage of antibody response to pneumococcal antigen serotypes for all the patients was 33% (Table 1). There was a significant rate of decreased antibiotic prescriptions after the intervention in patients treated with immunoglobulin supplementation (*n*=11; *p* = 0.0004) found by using a paired *t*-test (Table 2).

In addition, there was a statistically significant decreased rate of antibiotic prescriptions after the intervention with patients on prophylactic antibiotics (*n* = 5; *p* = 0.01). There

Table 2 Number of infections per year in each treatment arm

	Treatment Arm		
	Clinical Observation (<i>n</i> = 10)	Prophylactic Antibiotics (<i>n</i> = 5)	Immunoglobulin Therapy (<i>n</i> = 11)
Preintervention infection rate, no. infections/y	3.2	2.5	5.98
Postintervention infection rate, no. infections in the first year after interven- tion/y	2.5	0	1.6
<i>p</i>	0.28	0.01	0.0004

was not a statistically significant decrease in antibiotic prescriptions with the patients in the clinical observation arm ($n = 10$; $p = 0.28$) (Fig. 1). The comparison of the number of antibiotic prescriptions per year between the immunoglobulin supplementation arm and the clinical observation arm had a p value of 0.03, which indicated a statistically significant difference in the number of antibiotic prescriptions. The comparison between the prophylactic antibiotic arm and the clinical observation arm revealed a p value of 0.0039, which showed a statistically significant difference in using prophylactic antibiotics to reduce the number of infections (Fig. 2).

Antibiotic prescriptions were used as a continuous variable. There was a p value of 0.1269 for the folded F test, which meant equal variances were assumed. With that assumption, the p value from the pooled t -test was used to determine group differences. The mean number of infections in the previous year of those with treatment compared with those who underwent clinical observation was not statistically different. The mean difference in antibiotic prescriptions in those patients treated with immunoglobulin supplementation versus prophylactic antibiotics was not statistically significant ($p = 0.21$). The decision for clinical observation, prophylactic antibiotic therapy, or immunoglobulin supplementation was made at the individual immunologist's clinical discretion.

DISCUSSION

One of the important treatments for SAD is aggressively and adequately treating infections that occur. However, there is no consensus on long-term management of this disease. This study showed that, for patients diagnosed with SAD, there was a notable and statistically significant difference in antibiotic prescriptions per year in treatment with immunoglobulin supplementation or prophylactic antibiotics compared with the clinical observation arm. This finding was

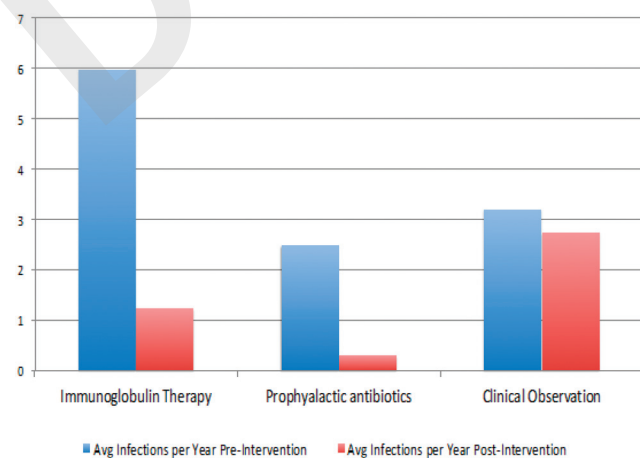


Figure 1. Average number of infections per patient in the first year before and after treatment.

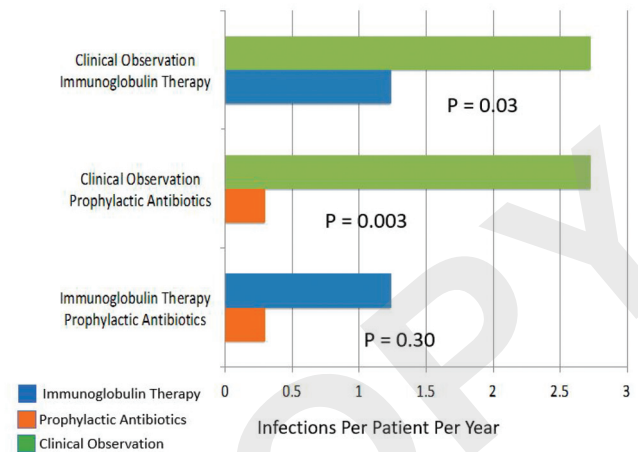


Figure 2. Comparison of treatment regimen on infections per year in all three treatment groups.

supported by a recent study that compared prophylactic antibiotics to immunoglobulin supplementation in patients diagnosed with SAD, with a mean age of 18 years and compared only prophylactic antibiotics and immunoglobulin supplementation therapy.¹¹ However, no notable difference was observed in antibiotic prescriptions between the immunoglobulin supplementation arm and the prophylactic antibiotic arm. Previous studies demonstrated that prophylactic antibiotics are a particularly effective strategy for managing younger patients with SAD, who are more likely to outgrow the disease.¹²

Currently, there is little evidence to guide the immunologist on the management of prophylactic antibiotic therapy in patients with SAD. The optimal antibiotic choice has not been determined. In addition, data are lacking with regard to the use of immunoglobulin supplementation in patients with SAD. Expert recommendations have noted that patients with SAD may benefit from immunoglobulin supplementation therapy for a brief period, although those time parameters have not been defined.¹ Currently, the dose of immunoglobulin supplementation recommended for SAD is the same dose used to treat other primary immunodeficiencies, *e.g.*, common variable immunodeficiency. Many centers use immunoglobulin supplementation for a 6- to 12-month duration before assessing the response to therapy. Limited pediatric studies have demonstrated the benefit of immunoglobulin supplementation for patients with SAD,¹³ but data are lacking on the use of prophylactic antibiotics for this population. Studies of patients with the diagnosis of chronic rhinosinusitis and co-existing SAD found benefit with the use of immunoglobulin supplementation.¹⁴ Some studies suggest that patients with fewer antibody responses to polysaccharide antigen vaccination may receive more of a benefit with immunoglobulin supplementation therapy.^{15,16} This possibility raises the question of whether

treatment of this disease should be determined based on the degree of antibody response impairment.

The average cost of immunoglobulin supplementation per patient per year is estimated to be approximately \$30,000, not including the costs of the initial testing of the disease.^{17,18} However, the cost of immunoglobulin supplementation could now be higher, given that the data for this statistic was collected in 2011. Also, this estimate does not take into account the cost of unscheduled visits, emergency department visits, hospitalizations, or bronchiectasis treatment that can occur for any patient with SAD.¹⁹ In addition, the use of immunoglobulin supplementation requires significant time and effort on the patient's part. The patient must be willing and able to inject him- or herself to receive subcutaneous infusions. For intravenous infusions, the patient must have access to an infusion center or home health for home infusions. Both subcutaneous and intravenous infusions require a time commitment from the patient. In addition, with the national shortages of immunoglobulin supplementation, it may become even more prudent to ensure that a patient truly requires immunoglobulin supplementation for his or her disease.²⁰ Additional cost-benefit studies are needed to gain more information.

This study had many limitations. The small number of patients in the study potentially limited the statistical power. In addition, the antibiotic prescription rate was determined purely through reviewing each chart and documenting the number of prescriptions. The study was not blinded and had the potential for reviewer bias. Antibiotics that may have been prescribed outside this medical center's pharmacy would not have been included. In addition, because antibiotics are often prescribed based on patient's symptoms, the majority of patients diagnosed with an infection and given an antibiotic did not undergo objective testing, such as sputum culture or nasopharyngeal swab, or radiography (e.g., chest radiography or computed tomography). Also, resolution of the antibody deficiency was not assessed in any of the patients described in this study. There was not a period during which antibiotics were discontinued, and infection frequency was monitored.

Currently, there are limited published data that compared the cost between immunoglobulin therapy and prophylactic antibiotics for patients with SAD. However, as mentioned earlier, immunoglobulin therapy can cost upward of \$30,000 per patient per year, and typical prophylactic antibiotic regimens similar to those used in patients with SAD can cost \$1000–3000 per patient per year.²¹ The estimate of the cost of prophylactic antibiotics was determined from a study of patients with known liver cirrhosis who required prophylactic antibiotic therapy to prevent spontaneous bacterial peritonitis.^{21,22} The exact cost of prophylactic antibiotic prescriptions for patients with immunodeficiency has not been studied.

CONCLUSION

Further studies should be conducted to assess best practice management and cost-effective strategies with regard to the treatment of SAD. However, this study provided a basis to argue for initially managing SAD with prophylactic antibiotics rather than initiating immunoglobulin supplementation after the diagnosis.

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