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Assessing the Immunogenic Response of A Single Center's Pneumococcal Vaccination Protocol In Sick Cell Disease

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Abstract

Sickle cell disease (SCD) is the most common inherited hematologic disorder in the United States. Patients with SCD are at increased risk of invasive pneumococcal disease (IPD) and are reliant on both early penicillin prophylaxis and anti-pneumococcal vaccination for prevention of infection. Although studies examining vaccine response have demonstrated a drop off of titer response after 3 years, an optimal vaccination regimen has not been identified. Our study sought to assess the immunogenicity of our center's pneumococcal vaccination strategy which included Prevnar® (PCV-7) (prior to the introduction of PCV-13) followed by Pneumovax® (PPV-23) given routinely at 2 and 5 years of age and then every 5 years thereafter. Our goal was to assess vaccine response in a population of patients with SCD who had received vaccines according to this regimen using multiplex bead analysis. Our study demonstrated a significant percentage of persons with SCD do not maintain a sufficient vaccination response to PPV-23 for 5 years. Our study revealed that only 36% of patients had protective levels of anti-pneumococcal antibody titers at an average of 37 months following vaccination. Most alarmingly, within the group of patients with sub-therapeutic titers, 64% demonstrated vaccine response to less than 25% of the tested serotypes. These findings were significantly associated with duration of time since last vaccine administration but the mean age of lack of response was below the 3-year window where vaccine response was previously reported to wane. Our results indicate anti-pneumococcal immunity may not be optimally maintained using this vaccination strategy in patients with SCD leaving them vulnerable to IPD. Many pediatric hematologists stop prophylactic penicillin at 5 years of age making these results alarming. We recommend further investigation into an optimal vaccine schedule and monitoring of anti-pneumococcal titers in at risk patients.

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Keywords

Sickle Cell Disease; PPV-23; PCV-13; PCV-7; Vaccine Response; Immunogenicity; Invasive Pneumococcal Disease

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Introduction

Sickle cell disease (SCD) is the most common inherited hematologic disorder in the United States (US). Prior to the advent of newborn screening, over 50% of affected patients died before 5 years of age. Due to early diagnosis and improved preventative care, over 95% of children are surviving into adulthood [1-3]. Previous studies have established that individuals with SCD have a higher risk of certain infections, particularly by encapsulated bacteria such as *Streptococcus pneumoniae* [4]. Prior to the initiation of newborn screening for SCD, infection due to *S. pneumoniae* was the leading cause of death in afflicted children, resulting in a mortality rate greater than 50% [4-7]. As a result of this increased risk, children with SCD are heavily reliant on both early penicillin prophylaxis and anti-pneumococcal vaccination for prevention of invasive pneumococcal disease (IPD) [7-9].

In standard pediatric practice, all children are supposed to receive conjugate anti-pneumococcal vaccination, Prevnar® (PCV-13), in addition to other routine immunizations. Current guidelines released by the National Heart Lung and Blood Institute (NHLBI) recommend that children with SCD also receive the 23-valent polysaccharide anti-pneumococcal vaccine, Pneumovax® (PPV-23), at 2 and 5 years of age [10]. Further recommendations regarding additional doses of PPV-23 are not specified. Studies show that up to 69% of pediatric hematologists stop penicillin prophylaxis and rely on these immunizations to prevent IPD after age 5 [11]. However, it remains unclear which patients maintain their vaccination response as they age, representing a clinical concern for many years [12-14]. Research on the efficacy, benefit, and duration of this regimen has not been performed and is especially important as patients with SCD are living longer.

Materials and Methods

Study Design and Participants

Records were obtained in an IRB approved, cross-sectional study, performed at the Sickle Cell Center of Southern Louisiana from July 2012 to July of 2013. To be included, patients had to have a confirmed diagnosis of SCD (all genotypes) and had to have been seen in the SCD clinic during the target 12-month period. In addition, all patients had to have undergone vaccination response testing during this time period (which was performed as part of the routine comprehensive assessment in this center). Patients who had undergone stem cell transplant or had received (non-autologous) immunoglobulin were excluded. Patients without a known immunization history were also excluded.

Data Collection

Demographic data (age, gender, and SCD genotype), immunization history, and routine blood work (CBC, LDH, and reticulocyte count) results were collected in addition to the patients' anti-pneumococcal immunoglobulin titers.

Standard Vaccination Practice (at the Sickie Cell Center of Southern Louisiana)

At the Sickie Cell Center of Southern Louisiana, PPV-23 is administered at ages 2 and 5 and was then re-administered every 5 years thereafter as a preventative measure given the high burden of IPD in the SCD population. At the time this study was conducted, older patients who did not receive either of the PCV vaccines as children did not receive a dose of either PCV7 or PCV13 when the vaccines were subsequently licensed.

Vaccination Response Assessment

Immunoglobulin titers were measured by ARUP laboratories using quantitative multiplex bead assay [15-16]. Luminex multiple analyte profiling involves a flow cytometric system that allows for single sample testing against multiple analytes. This technique utilizes competitive inhibition binding at various dilutions with 1-hour incubation periods in order to assess serum immunogenicity against a wide array of pneumococcal serotypes [15].

Interpretation of Vaccine Response

It was necessary to define individual patients' immune responses both per serotype as well as to define "overall vaccination response." For each specific serotype, adequate immune response was defined as greater than 1.3 mcg/mL as per the laboratory testing guidelines [17]. We classified patients as "good responders" if their serum levels of IgG were ≥ 1.3 mcg/mL to at least 50% of the 23 pneumococcal serotypes tested (i.e. >12 serotypes with levels of greater than 1.3 mcg/mL). Poor vaccine responders were defined as those who responded to 11 or less of the designated serotypes. An appropriate antibody response to 50-70% or more of the serotypes is thought to represent a normal humoral response based on previous reports although these criterion are arbitrary and other studies suggest a more aggressive cut-off [18].

Statistical Analysis

Patients were categorized into good and poor responders as per definitions above. Spearman's Correlation Coefficient was used to assess the association between the percent of serotypes to which patients responded and selected demographic and clinical variables. Differences in demographic and clinical variables between these two groups of responders were assessed using Pearson's χ^2 test (categorical variables) and Analysis of Variance (ANOVA) for continuous variables. ANOVA results were confirmed with the Kruskal-Wallis test when normality assumptions were questionable. In all cases, results were consistent between alternative tests.

Results

Data were originally collected on a total of 66 patients with SCD. The majority (45) of patients had HbSS disease. There were 37 male patients and 29 female patients. The average age of this cohort of patients was 10.9 years, with a range of 1-22 years (table I). Within our cohort of 66 patients, 64% (42/66) had received both the PCV-7 series and the PPV-23. However, 33% of the cohort (older patients) had only received PPV-23 since the PCV-7 series of vaccines was unavailable until after 2000. This study was conducted during prior to the initiation of PCV-13. Please see table I for further demographic information.

Within the cohort of 66 patients who had received the PPV-23 vaccine, only 36% (24/66) were classified as good responders (adequate protection to at least 50% of the 23 serotypes). The remaining 64% of patients (42/66) demonstrated a poor vaccination response. Within the poor responding group, a large percentage of the patients, 64% (27/42), responded to less than 25% of all serotypes. In this group of patients with the worst response, the majority (81.5%) had received their last PPV-23 over 36 months before antibody testing ($p<0.0001$). There was no statistical difference in the average age of patients with poor versus good vaccination response (supplemental table I). Those who demonstrated good response to PPV-23 were slightly younger, with an average age of 10.4 years (± 5.7) versus 13.0 years (± 5.4) for those patients with poor response (table II).

There was no difference in immunization response between patients who received the conjugate vaccine series (PCV-7) and the polysaccharide vaccine (PPV-23) and those who only received only PPV-23. In addition, there were no differences in vaccination response seen in patients who had received only one PPV-23 or those who had received multiple PPV-23 vaccines.

Additional variables assessed as part of the initiative included SCD genotype, baseline hemoglobin and baseline lactate dehydrogenase level (table III). These variables were not predictive of vaccination response. Time since last PPV-23 was highly predictive in all statistical analyses.

Discussion

Patients with SCD remain at lifelong risk of IPD but penicillin prophylaxis and newborn screening for SCD has dramatically reduced childhood mortality [19]. Clinical practice has shifted towards stopping antibiotic prophylaxis at 5 years of age under the assumption that patients are protected by the current NHLBI anti-pneumococcal vaccine regimen [10, 20]. Patients with SCD are now living into adulthood making it imperative that we assess their lifetime immunogenicity and risk of IPD as no studies have identified an optimal vaccination schedule.

Prior Studies in Vaccine Response

Previous studies have demonstrated that PCV-7 and PCV-13 elicit antibody responses against all covered serotypes and are notable for their safety in both pediatric and adult populations [18-22]. Similar research has also demonstrated efficacy of PPV-23 in

preventing IPD in asplenic older adults [21, 23]. Persons with SCD differ from healthy adults in that they are likely to be without a functional spleen due to auto-infarction or hypersplenism throughout their lifetime [24].

The immunogenicity of anti-pneumococcal vaccination regimens in SCD remains debated and is worthy of review. An early study examining vaccine response to PPV-23 in pediatric patients with SCD demonstrated a marked drop-off in antibody titer level 3 years after administration [25]. However, this study used older methods of antibody analysis that has been proven to be less serotype specific (compared to our study). An additional study evaluated the use of booster PPV-23 immunization in patients with SCD and found a marked increase in antibody level without associated adverse reactions [23]. Finally, a recent study published by De Montalembert et al. assessed vaccination response to PPV-23 in children with SCD [26]. However, this study focused only on analysis of titers at 1 month and 1 year and provides no firm recommendations for repeat administration of PPV-23 after 5 years of age in the recently released guidelines by the NHLBI [10].

These findings are of significance in that multi-year cohort studies from Jamaica have demonstrated that patients with SCD remain susceptible to *S. pneumoniae* infection when their penicillin prophylaxis is stopped [27]. These studies demonstrated a marked rise in IPD upon the cessation of penicillin prophylaxis (despite standard anti-pneumococcal vaccination) indicating that routine vaccination against *S. pneumoniae* may be insufficient [27]. Thus, affected individuals remain susceptible to infection, which may be due (in part) to lack of persistent anti-pneumococcal titer response [28-29].

Monitoring Anti-pneumococcal Antibody Titers

This study also highlights the importance of monitoring anti-pneumococcal titers as a method of determination of optimal timing of re-vaccination to prevent hypersensitivity reactions. Due to concerns with B cell exhaustion from excessive vaccination with pneumococcal polysaccharide vaccination, this will need to be studied closely as literature in adults has previously identified this as a problem [29]. Finally, while the creation of a universal pneumococcal antigen-based vaccine would render the utility of titer measurement unnecessary, these trials are still in their infancy and are likely not close to widespread use globally.

Study Limitations

This study was limited as it is both retrospective and cross-sectional; therefore it only assessed vaccination response at one point in time. To fully assess individual vaccine response, both pre and post vaccination samples need to be obtained for comparison. Ideally, post-vaccination samples should be obtained at 4 to 6 weeks post-immunization and should demonstrate a minimum of a 2-4-fold increase to be considered an appropriate response [30]. An additional limitation of our study is that not all patients received either PCV-7 or PCV-13, due to their ages, which should be considered in assessing immunity in older patients. Finally, lab analysis of immunogenicity is highly variable in existing literature with many studies utilizing EILSA and radioimmuno-assay (RIA), which cannot differentiate IgM and IgG antibody [31-34]. Recent evidence demonstrates the superiority of using

quantitative multiplex bead analysis for more specific results of IgG antibody quantitation compared to both the ELISA and RIA methods which is why it is preferentially used at our center [16]. These results were also controlled against the United States Food and Drug Administration's (USFDA) pneumococcal serology reference standard. However, comparative normal ranges for this assay apply to vaccinated adults without SCD, as healthy children do not typically receive PPV-23 making generalization difficult.

Conclusion

Despite the limitations of this study, our data demonstrates that many individuals with SCD remain under-immunized (and presumably under-protected) against IPD. This study utilized a liberal definition of adequate vaccination response (i.e. IgG quantity of at least 1.3 mcg/mL to greater than 50% of serotypes). The definition of immune system competence per ARUP testing laboratories as an adequate response to at least 70% of the serotypes in the vaccine challenge for those 6-65 years of age, or to at least 50% of the serotypes in the vaccine challenge for those 2-5 years of age. Our study may have overestimated the number of "good" vaccination responders according to this definition making it possible that this study underestimated the degree to which patients with SCD are immune deficient in this area. Moving forward, it will be necessary to determine the response of re-vaccination in patients deemed insufficiently immunized. Future studies should also include a measure of opsonic activity and white blood cell function as well as antibody concentrations.

Finally, it is important to note that the majority of the antibody levels (IgG) in this cohort (to all serotypes) were far below those obtained in healthy historical control studies including those used by the USFDA's pneumococcal serologic reference standard. These results are alarming in that they indicate an abnormal immune response in patients with SCD not solely explained by loss of splenic function. Our data demonstrates that not only is standard of care vaccination with PPV-23 potentially inadequate, but our center's frequency of re-vaccination every 5 years thereafter is also insufficient in providing protective anti-pneumococcal titer levels in the majority of patients in our study. However, further studies must be undertaken before changing re-vaccination schedules as the concern for B-cell exhaustion in this patient population is a significant risk. A second prospective study evaluating secondary vaccination response to those patients who were initially defined as poor responders is forthcoming in order to better analyze the humoral immune capacity of the involved patients.

While this study did not assess for an increase or re-emergence of IPD, our findings reinforce the persistent risk for IPD in a susceptible population and until further data can be collected on an optimized anti-pneumococcal vaccination schedule, it is possible that patients with SCD should remain on continued antibiotic prophylaxis to prevent IPD and its sequelae but further prospective studies are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I**Demographics**

Variable	Range	N (cohort of 66)
Age	1-5 yrs	8
	6-10 yrs	18
	>10 yrs	39
Gender	Male	37
	Female	29
Genotype	HbSS	45
	HbSC	16
	HbSB+	5
Vaccine Received	PCV 7+PPV-23	42
	PPV-23 Only	24

Table II
Association between the percent vaccination response and selected demographic and clinical variables

Variable	ρ	P
Age	0.05	0.6693
Number of PS23 received	0.01	0.9676
Number of PCV7 received	0.01	0.9657
Time since last PS23	-0.48	<0.0001

Table III
Differences in demographic and clinical variables by responder category

	Vaccination Response		p(χ^2)
	Poor (n = 45)	Good (n = 21)	
Hb genotype			
SB	3	2	0.8336
SC	12	4	
SS	30	15	
Vaccines received			
PS23	18	6	0.3687
PCV7 + PS23	27	15	
Age (years)			
< 16	27	15	0.3687
16	18	6	
Time (months) since PS23			
36	11	12	0.0094
>36	34	9	

Age *	13.0 + 5.3	10.6 + 5.6	0.0911
Hb *	9.1 + 1.8	8.4 + 1.7	0.2164
LDH *	487.7 + 205.5	521.1 + 140.2	0.5655
Number of PS23 *	1.7 + 0.9	1.7 + 0.6	0.9080
Number of PCV 7 *	2.0 + 1.9	2.8 + 2.0	0.1573
Time since last vaccine *	47.3 + 18.3	27.5 + 24.1	0.0005

* Mean + SD