Prophylactic Penicillin After 5 Years of Age in Patients With Sickle Cell Disease: A Survey of Sickle Cell Disease Experts

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Background. Since the publication of the Prophlyactic Penicillin Study II in 1995, the management of penicillin prophylaxis for children with sickle cell disease (SCD) after 5 years of age has been controversial. In this study, we sought to describe current practice patterns of pediatric hematologists related to cessation of penicillin prophylaxis for children with SCD after 5 years of age. ***Procedure.*** We performed a cross-sectional, electronic survey of pediatric hematologists with expertise in SCD to examine practices regarding penicillin prophylaxis in children with SCD after 5 years of age. We also investigated factors potentially associated with continuation of penicillin prophylaxis using the Jonckheere–Terpstra test and Fisher's exact test. ***Results.*** Of the 106 physicians surveyed from 76 centers, 84% completed the survey. Among respondents, 76% routinely recommended cessation of penicillin prophylaxis after 5 years of age. The practice of routinely continuing penicillin after 5 years of age was associated with decreased concern about antibiotic resistance in *Streptococcus pneumoniae* ($P = 0.01$), with the usage of prophylactic penicillin in mild SCD genotypes (sickle hemoglobin-C disease and sickle β^+ thalassemia, $P = <0.001$), and with increasing use of other preventive evaluations (e.g., MRI for silent stroke) in childhood ($P = 0.05$). ***Conclusion.*** Most pediatric hematologists with an SCD expertise recommend cessation of prophylactic penicillin after 5 years of age. Pediatr Blood Cancer

Key words: invasive pneumococcal disease; penicillin prophylaxis; sickle cell disease; survey

INTRODUCTION

Children with sickle cell disease (SCD) are at markedly increased risk of infection due to *Streptococcus pneumoniae*, particularly during the first 5 years of life [1,2]. The risk is greatest in individuals with homozygous sickle cell anemia (HbSS) and sickle β^0 thalassemia (HbSβ^0) but may also be increased in sickle hemoglobin-C disease (HbSC) [3,4]. Functional asplenia, which occurs commonly by 2 years of age in children with HbSS and HbSβ^0 but infrequently in children under 5 years of age with HbSC, causes the risk for invasive pneumococcal disease (IPD) in SCD [5,6]. The Prophylactic Penicillin Study (PROPS) established prophylactic penicillin as standard care for children with HbSS and HbSβ^0 under 5 years of age [7]. A follow-up randomized clinical trial, the Prophylactic Penicillin Study II (PROPS II), was designed to address whether penicillin may be safely discontinued at 5 years of age and included 400 subjects for an average of 3.2 years [8]. PROPS II investigators predicted that IPD, the primary outcome, would occur in 4% of the penicillin continuation arm and 12% of the discontinuation arm. A smaller-than-expected number of IPD events, however, occurred in both arms of the study—two infections (1%) in the continuation arm and four (2%) in the discontinuation arm, a difference that was not statistically significant. The PROPS II authors concluded that penicillin prophylaxis may be safely discontinued at 5 years of age in HbSS patients without a history of surgical splenectomy or prior IPD. Although reassuring, the small number of IPD events led to uncertainty in the interpretation of PROPS II by pediatric hematologists. Therefore, more than a decade later, we aimed to describe practice patterns and their correlates for pediatric hematologists with SCD expertise regarding discontinuation of penicillin at 5 years of age in children with SCD.

METHODS

We conducted a cross-sectional electronic survey of pediatric hematologists in the United States with an expertise in SCD. The survey was up to 16 questions in length and typically required 5–10 minutes to complete (the full survey is available in the Supplemental Appendix). Consent for research participation was implied by survey completion. The Institutional Review Board of the University of Texas Southwestern Medical Center approved this study.

Study Procedures

An email of invitation including a survey link was sent to pediatric SCD experts in the United States who were identified by several methods. For subject identification, we included pediatric hematologists with an expertise in SCD known to the authors through publications, professional organizations, and research meetings. We also reviewed membership listings of the American Society of Pediatric Hematology-Oncology and Children's Oncology Group. From this review, physicians were included in the survey if they were listed in their medical center's website as the SCD program director. Centers without a website designation of an SCD program director were contacted by email or telephone to determine whether a physician in the practice had particular SCD expertise or directed an SCD program. To limit bias from inclusion of a few very large SCD centers, no more than three physicians from any center were surveyed. Personalized emails were sent to each physician on Week 0 and subsequently resent on Weeks 2, 6, and 10 to non-responders. Survey results were collected through the RedCAP system of UT Southwestern [9]. Responses were de-identified prior to data analysis. The survey instrument was reviewed by three pediatric hematologists (non-

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study personnel) prior to formal administration to assess for clarity and face validity. No assessment of test/re-test reliability was performed.

Analyses

Responses were included in the analysis if question 6, which asked about the typical practice regarding prophylactic penicillin past 5 years of age, was completed. Summary statistics included frequencies and cross-tabulations. The primary outcome was descriptive: the proportion of physicians reporting routine continuation of prophylactic penicillin beyond 5 years of age. Secondary outcomes included the respondents' rationale for their penicillin continuation/discontinuation practices. In exploratory analyses, the Jonckheere–Terpstra test and Fisher's exact test were used to evaluate associations between penicillin continuation practice and several potential correlates including: center attributes (number of total SCD patients, number of physicians involved in SCD care, non-physician personnel participating in SCD care), the respondent's screening practices, concern about antibiotic resistance, and concern for medication adherence. The final survey question was an open-ended prompt to provide free-text insights about penicillin prophylaxis past 5 years of age. The comments resulting from this question were analyzed for themes by all study team members. Included in the results are representative quotes which were identified independently by the three authors and agreed upon by all study team members. All quantitative analyses were completed with SAS 9.2 (SAS Institute, Gary, NC).

RESULTS

Sample Description and Survey Responses

A total of 106 physicians representing 76 centers were surveyed, and 89 respondents completed the survey (84% reply rate). Table I describes attributes of the responding physicians and centers. Respondents represented a wide distribution of SCD center sizes and geographic diversity with an expected over-representation of Southern states given the population distribution of SCD

TABLE I. Attributes of Responding Centers

Center attribute	All centers, percentage (N = 89)	Continue pen. past 5 yr, percentage (N = 21)	Discontinue pen. at 5 yr, percentage (N = 68)	*P*-value
How many children (18 yr and younger) with SCD are cared for at your center? (select one)				
<100	10.1	19.1	7.4	0.45
100–200	15.7	9.5	17.7	
200–300	22.5	19.1	23.5	
300–400	16.9	28.6	13.2	
400–500	9.0	4.8	10.3	
>500	25.8	19.1	27.9	
How many physicians routinely care for SCD patients in the clinic at your center? (select one)				
1	16.9	9.5	19.1	0.11
2	18.0	9.5	20.6	
3–4	32.6	42.9	29.4	
4–5	7.9	0	10.3	
6–7	13.5	19.1	11.8	
>7	11.2	19.1	8.8	
In which geographic region is your center located? (select one, N = 88)				
Northeast	22.5	33.3	19.1	0.11
South	39.3	23.8	45.6	
Midwest	20.2	14.3	22.1	
West	16.9	28.6	13.2	
What non-physician personnel are involved exclusively in your SCD program? (select any that apply)				
Nurse	82.0	90.5	79.4	0.37
Nurse practitioner	80.9	80.9	80.9	
Chronic transfusion nurse	37.1	57.1	32.4	
Social worker	84.3	81.0	85.3	
TCD tech/nurse	34.8	23.8	38.2	
Psychologist	46.1	57.1	42.7	
Do you routinely recommend (at any age) the following preventive evaluations for HbSS patients in your practice? (select any that apply)				
Transcranial Doppler ultrasound for stroke risk	96.6	95.2	97.1	0.05
Urinalysis for sickle nephropathy	92.1	95.2	91.2	
Echocardiography for elevated TR jet velocity	76.4	90.5	72.1	
Pulmonary function tests for asthma	65.2	71.4	63.2	
Imaging for hip avascular necrosis	15.7	28.6	11.8	
MRI of brain for silent stroke	28.1	42.9	23.5	

SCD, sickle cell disease; N, number; TCD, transcranial Doppler ultrasonography; HbSS, sickle cell anemia; TR, tricuspid regurgitant; MRI, magnetic resonance imaging.

in the US [10]. Over 80% of respondents report having an SCD-specific nurse, nurse practitioner, and social worker while less than half report having an SCD-specific psychologist, chronic transfusion nurse, and TCD tech/nurse. Other personnel reported included a genetic counselor (n = 4), teacher (n = 1), psychometrist (n = 1), and dietician (n = 1). In addition to the routine screening tests selected in the survey, respondents reported the routine use of ophthalmologic examinations (n = 7), gall bladder ultrasonography (n = 3), vitamin-D levels (n = 1), bone density evaluation (n = 1), and priapism screening (n = 1).

For the primary descriptive outcome, 23.6% (N = 21) of respondents routinely recommend continuation of penicillin past 5 years of age for children with HbSS (Table II). Among those recommending continuation of penicillin (N = 21), 100% endorsed a decrease in the incidence of IPD and 33% endorsed a decrease in other bacterial infection as the rationale. Among respondents who routinely recommend discontinuation of penicillin at 5 years of age (N = 68), 91% endorsed the results of the PROPS-II study and 50% endorsed expert opinion as contributors to the rationale for penicillin discontinuation. In the discontinuation group, prior history of surgical splenectomy or IPD would prompt nearly 90% to continue penicillin prophylaxis.

The survey addressed other facets of physician attitudes and practices relating to penicillin continuation (Table III). Concern about inducing penicillin resistance was evenly distributed across answer choices ''not concerned,'' ''slightly concerned,'' and ''somewhat concerned''; none of the respondents reported that they were ''very concerned.'' Approximately 90% of all respondents reported addressing penicillin adherence by asking parents about the frequency of missed doses and reminding them about the increased risk of IPD in HbSS. Over 75% of all respondents mentioned being ''slightly concerned'' or ''somewhat concerned'' regarding poor adherence. In considering patients with less severe sickle genotypes [HbSC and sickle β^+ thalassemia (HbSβ^+)], 90% of all respondents recommended penicillin for both genotypes or HbSC alone during the first 5 years of life, whereas only 18% recommended continuing penicillin for both genotypes or HbSC alone after 5 years of age.

Analyses of Association With Penicillin Continuation

In exploratory analyses (Tables I and III), we found no association between the continuation of penicillin past 5 years of age and the number of patients at a center, the number of non-physician personnel at a center, the penicillin prescription provider, the concern about medication adherence, and the practice of penicillin prophylaxis under 5 years of age for mild sickle genotypes. The continuation of penicillin past 5 years of age in children with HbSS was associated with less concern about induction of penicillin resistance, the continuation of penicillin prophylaxis past 5 years of age for mild SCD genotypes, and higher number of preventive evaluations.

Qualitative Responses

The final survey question asked for any other insights on the continuation of penicillin past 5 years of age. From these responses, three primary themes were identified: (1) PROPS-II was not adequate to conclude that stopping penicillin is safe. ''The PROPS-II study only followed patients for a few years. The inability to show the benefit of penicillin prophylaxis versus placebo for children over 5 years age who were followed for only a couple of years,

TABLE II. Practice of Prophylactic Penicillin Past 5 Years of Age

Center attribute	Percentage
Do you routinely recommend continuation penicillin at 5 years of age for children with HbSS? (select one, N = 89)	
Yes	23.6
No	76.4
Restricted to ''no'' responses for continuing penicillin past 5 years of age	
What is your rationale for recommending discontinuation at 5 years of ? (select any that apply, N = 68)	
Supported by expert opinion	50.0
Supported by results of PROPS II study	91.2
Continuing penicillin creates unnecessary expense	5.9
Continuing penicillin is an inconvenience for families	16.2
Continuing penicillin encourages emergence of resistance	26.5
Continuing penicillin requires time to address adherence	4.4
Under what circumstances would you recommend continuing penicillin past 5 years of age? (select any that apply, N = 68)	
Prior history of surgical splenectomy	89.7
Prior invasive *S. pneumoniae* infection	91.2
Overall severe clinical course	10.3
Parents strongly desire to continue prophylaxis	67.6
Incomplete PCV series	45.6
No history of receipt of PPV series	52.9
Restricted to ''yes'' responses	
What potential benefits cause you to usually recommend continuing penicillin past 5 years of age? (select any that apply, N = 21)	
Reduced incidence of invasive *S. pneumoniae* infection	100
Reduced incidence of other bacterial infections	33.3
Reduced incidence of acute chest syndrome	0
Reduced incidence of vaso-occlusive crises	0

HbSS, sickle cell anemia; N, number; PROPS II, Prophylactic Penicillin Study II; PCV, pneumococcal conjugate vaccine; PPV, pneumococcal polysaccharide vaccine.

TABLE III. Penicillin Adherence, Resistance, and Use in Mild SCD Genotypes

Center attribute	All centers, percentage (N = 89)	Continue pen. past 5 yr, percentage (N = 21)	Discontinue pen. at 5 yr, percentage (N = 68)	*P*-value
For most HbSS patients in your practice, who provides the prescription for penicillin? (select one)				
You (your practice)	77.5	76.2	77.9	0.29
PCP	0	0	0	
Both	21.3	19.1	22.1	
How do you (or members of your practice) monitor and encourage adherence to penicillin? (select one, N = 69)				
I ask the caregiver about the frequency of missed doses	88.4	81.3	90.6	0.38
I remind the parents of the ↑ risk of IPD for children with HbSS	94.2	93.8	94.3	0.99
I ask the caregivers to bring their bottles to clinic	2.9	6.3	1.9	0.41
I do not monitor adherence	2.9	0	2.9	0.99
How concerned are you for suboptimal adherence for patients who continue penicillin past 5 years of age? (select one)				
Not concerned	9.0	9.5	8.8	0.37
Slightly concerned	24.7	33.3	22.1	
Somewhat concerned	53.9	47.6	55.9	
Greatly concerned	12.4	9.5	13.2	
How concerned are you about inducing resistance in *S. pneumoniae* if patients continue prophylactic penicillin past 5 years of age? (select one)				
Not concerned	30.3	52.4	23.5	0.01
Slightly concerned	32.6	28.6	33.8	
Somewhat concerned	33.7	19.1	38.2	
Greatly concerned	3.4	0	4.4	
Do you routinely recommend penicillin for patients with HbSC and HbSβ^+ thalassemia *under* 5 years of age? (select one, N = 87)				
No	10.3	5.0	11.9	0.38
Yes for SC only	5.8	0	7.5	
Yes for Sβ^+	0	0	0	
Yes for SC and Sβ^+	83.9	95.0	80.6	
Do you routinely recommend penicillin for patients with HbSC and HbSβ^+ thalassemia *over* 5 years of age? (select one, N = 89)				
No	82	28.6	98.5	<0.001
Yes for SC only	2.2	9.5	0	
Yes for Sβ^+	0	0	0	
Yes for SC and Sβ^+	15.7	61.9	1.5	

SCD, sickle cell disease; HbSS, sickle cell anemia; PCP, primary care provider; N, number; IPD, invasive pneumococcal disease; HbSC, hemoglobin SC disease; HbSβ^+, sickle beta-plus thalassemia.

is not evidence that penicillin prophylaxis is not beneficial for the lifetime of the patient." (2) Physicians desire to increase patient autonomy by reviewing the risks and benefits and not making a formal recommendation. "I provide the caregivers with the data on over 5 years and let them make the decision... I I don't make a recommendation." (3) The importance of penicillin for IPD is decreased due to the success of currently available vaccines. "I'm less worried about parents who refuse to give it than I was in the pre-Prevnar (pneumococcal conjugate vaccine) days."

DISCUSSION

We report the results of a survey of pediatric hematologists with SCD expertise to define practices of continuation versus cessation of penicillin prophylaxis at 5 years of age. SCD experts were sampled because their practice patterns would be more likely to be informed by the relevant literature and clinical experience when compared to other pediatric hematology–oncology specialists or general pediatricians. The excellent response rate (84%) suggests this topic is important to physicians involved in the care of children with SCD. The primary finding was that most physicians who specialize in SCD care routinely recommend cessation of prophylactic penicillin at 5 years of age for children with HbSS.

When an evidence base is limited, divergent practices among specialists are expected. PROPS-II is the only study to assess the safety of cessation of penicillin at 5 years of age. Interestingly, the conclusions of PROPS-II have not been meaningfully disputed in the published medical literature. In a recent report evaluating the quality of the medical literature comprising the evidence base in SCD, the authors quoted the conclusions of the PROPS II study that prophylactic penicillin may thus be safely discontinued at 5 years of age [11]. Similarly, in a 2002 Cochrane Review, the authors argue that the IPD incidence rates observed in the PROPS II trial (0.67/100 patient years in the placebo group, 0.33/100 patient years in the penicillin group) are low enough to justify routine cessation of penicillin past 5 years of age [12]. The respondents in this study demonstrated awareness of the limitations of PROPS-II and expressed nuanced rationale for their individual practice. The differences between the literature and practice may reflect both the scant evidence base surrounding this topic and the relative inability of the literature to adequately capture the nuance in treatment decisions. Until better evidence exists, consistent practice among experts is unlikely to be achieved.

Since the completion of PROPS-II, additional data have become available that may influence decision-making on penicillin cessation at 5 years of age. First, although the incidence of IPD has dramatically decreased in children under 5 years of age following the licensure of the heptavalent pneumococcal conjugate

vaccine (PCV7) in 2000 [13,14], no significant decrease in IPD incidence in HbSS patients over 5 years of age was observed. Also, the most recent estimates of IPD incidence in HbSS patients over 5 years of age in the post-PCV7 era were 0.1/100 patient years [13] and 0.19/100 patient years [15] which remain 25- to 50-fold higher than current IPD incidence rates for the general population, 0.003/100 patient years [16]. Finally, in the mid-1990s, increasing penicillin resistance was observed in pneumococcal isolates which may have prompted providers to more readily accept the conclusions of PROPS-II and to stop penicillin to avoid inducing resistance [17–19]. The increase in penicillin resistance, however, has not continued in the 2000s [20–22]. The low incidence and absolute risk of IPD in HbSS may influence providers to discontinue penicillin while the large relative risk of IPD (compared to the general population) may influence providers to continue penicillin more frequently.

The association of penicillin continuation with increased use of preventive evaluations is noteworthy. Like continuation of penicillin, routine screening echocardiography, and brain MRI in childhood are controversial and lack a strong evidence base. Until the results of the Silent Infarct Transfusion trial [23] are known, limited evidence supports the practice of routine screening MRI. Yet, nearly half of SCD experts who continue penicillin past 5 years of age obtain screening MRI's compared to 23% of those who do not recommend penicillin. This finding suggests that physicians who recommend continuation of penicillin are more likely to recommend other screening strategies and preventive evaluations. This may be attributable to an overall more cautious approach by certain physicians/centers or to philosophical differences in the approach to ''comprehensive'' subspecialty care.

This study is limited by factors inherent to the survey methodology. Respondents may not be representative of non-respondents and thereby introduce bias. Similarly, we have no means of confirming the accuracy of the responses provided which may have been affected by recall bias and social desirability bias. Additionally, our method for identifying potential respondents may have excluded legitimate SCD experts whose views were not represented in this survey. Additionally, the validity of the survey instrument was not established by test/re-test reliability. Finally, due to concern about recall bias, we did not assess the frequency of IPD cases in the past 5 years or the penicillin resistance trends at individual centers, both of which may have shaped individual practices. Also, no assessment was made of the relative importance of penicillin cessation at 5 years of age for the future SCD research agenda which may have clarified the possibility of completing subsequent studies.

In conclusion, the findings of this survey provide insights into the current state of care provided to patients with SCD. Most SCD experts recommend cessation of penicillin prophylaxis at 5 years of age, with advocates on both sides of the issue demonstrating familiarity with the PROPS-II controversy. Due to the rarity of IPD with modern vaccines, the feasibility of prospectively assessing the efficacy of penicillin to prevent IPD beyond 5 years is limited. Therefore, providers will continue to be tasked with interpreting limited data to generate recommendations for patients and their caregivers.

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