JPPT | Single-Center Retrospective Study

Penicillin Prophylaxis in Patients With Sickle Cell Disease Beyond Age 5 Years

Tyler G. Eastep, PharmD; Rebecca M. Kendsersky, PharmD; Jessica Zook, PharmD and Astrela Moore, PharmD

OBJECTIVE Patients with sickle cell disease (SCD) are at increased risk for invasive pneumococcal disease (IPD) caused by *Streptococcus pneumoniae*. Immunization and antimicrobial prophylaxis may prevent this complication, and landmark clinical trials support discontinuation of antimicrobial prophylaxis at age 5 years. However, antimicrobial prophylaxis continues in some patients indefinitely. The objective of this study was to evaluate the incidence of culture-positive IPD and other infections in the setting of penicillin prophylaxis in the pediatric SCD population.

METHODS This was a single-center, retrospective cohort study of patients with SCD who continued antimicrobial prophylaxis with penicillin, compared with those whose antimicrobial prophylaxis was discontinued. Included patients were aged 5 to 18 years during the study period and had no history of IPD or surgical splenectomy. Patient charts were reviewed for demographics, immunizations, penicillin prescription history, and microbiologic culture data.

RESULTS Antimicrobial prophylaxis continued beyond age 5 years in 65% of patients, a higher percentage of whom had hemoglobin SS or S beta-zero disease. No patients whose antimicrobial prophylaxis was discontinued experienced IPD; 1 patient who continued antimicrobial prophylaxis died of *S pneumoniae* sepsis. Rates of other infections were comparable between groups (21% in prophylaxis versus 18% in no prophylaxis).

CONCLUSIONS These results support appropriate de-prescribing of antimicrobial prophylaxis in patients with SCD who are not at high risk for IPD. Further multicenter studies are needed to evaluate consequences of antimicrobial prophylaxis with alternative agents on antibiotic resistance, examine provider rationale for continuation of antimicrobial prophylaxis, and assess quality of life effects (e.g., medication adherence, adverse drug reactions) of antimicrobial prophylaxis.

ABBREVIATIONS HbS, hemoglobin S mutation; ICD, International Classification of Disease; IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PCV-7, pneumococcal conjugate vaccine, 7-valent; PCV-13, pneumococcal conjugate vaccine, 13-valent; PPSV-23, pneumococcal polysaccharide vaccine, 23-valent; PROPS, Prophylaxis with oral penicillin in children with sickle cell anemia; SB0, hemoglobin S beta-zero disease; SCD, sickle cell disease; SS, hemoglobin SS disease

KEYWORDS anemia; sickle cell; antibiotic prophylaxis; antimicrobial stewardship; hematology; pediatrics; pneumococcal infections; pneumococcal vaccines

J Pediatr Pharmacol Ther 2023;28(6):519–523

DOI: 10.5863/1551-6776-28.6.519

Downloaded from http://meridian.allenpress.com/jppt/article-pdf/28/6/519/3288872/i2331-348x-28-6-519.pdf by guest on 22 February 2024

Introduction

Sickle cell disease (SCD) is a heritable disorder caused by gene mutations that lead to malformation of red blood cells. The genes implicated in SCD include hemoglobin S, C, beta-zero, and beta-plus, which affect the formation of beta globin, a protein subunit of hemoglobin. These mutations cause substitution of a hydrophilic amino acid residue for one that is hydrophobic, leading to sickling, where the biconcave disc-shaped erythrocytes become flattened and brittle. This change in structure leads to a shortened cellular lifespan that predisposes individuals to small vasculature occlusion.[1] Patients who are homozygous for the sickled hemoglobin gene (HbS) typically have the most severe presentation. Acute complications include pain crises, stroke, and invasive pneumococcal infections such as bacteremia, meningitis, and pneumonia, which are namely due to development of asplenia.

As SCD progresses, children gradually lose splenic function owing to vaso-occlusion leading to tissue ischemia. The spleen is involved with the opsonization of encapsulated pathogens, a complement-mediated process that tags them for removal by phagocytosis.[2] Hyposplenia or asplenia limits this process and

consequentially blunts the immune response against a nascent infection. The functional asplenia seen in patients with SCD thus leaves them at particular risk for invasive infection due to encapsulated organisms, including *Streptococcus pneumoniae*. In the absence of a functional spleen, this blunted infectious response is typically overcome via acquired immune function that develops throughout childhood. A lack of acquired immunity leaves younger children at highest risk. Accordingly, the case-fatality rate of pneumococcal bacteremia in children with SCD younger than 3 years is reported to be as high as 24%.[2] Aside from the passage of time, another crucial intervention for reducing the incidence of pneumococcal infection is the proliferation of pneumococcal conjugate vaccines (PCVs). Studies have shown not only a reduced incidence of invasive pneumococcal disease (IPD) in older pediatric patients, but also the incidence has further declined following the uptake of newer iterations of pneumococcal vaccines (PCV-13) that cover a broader range of serotypes.[3,4] Pneumococcal polysaccharide vaccine, 23-valent (PPSV-23) is recommended in patients with SCD to confer further protection against pneumococcal infections, but no data exist that specifically evaluate the uptake of this vaccine and its effectiveness at preventing IPD.[5]

In addition to vaccinations, another critical intervention for the prevention of IPD is antimicrobial prophylaxis against *S pneumoniae*. The Prophylaxis with oral penicillin in children with sickle cell anemia (PROPS) trial[6] established the efficacy of antimicrobial prophylaxis with penicillin at preventing IPD, and the follow-up PROPS-II study[7] demonstrated the safety of discontinuation in patients following their fifth birthday (absent any prior IPD or splenectomy). On the basis of these 2 studies, the national Evidence-Based Management of SCD Expert Consensus Report recommends the discontinuation of penicillin prophylaxis at age 5 years, with the exclusion of patients with surgical asplenia or a prior invasive pneumococcal infection.[8] Conversely, the guidelines maintained by the British Society for Standards in Hematology recommend lifelong penicillin prophylaxis in high-risk patients, which includes patients with surgical asplenia, prior IPD, age less than 16 years, and age greater than 50 years, citing literature in the non–sickle cell population with hyposplenia or asplenia. Notably, these guidelines include recommendations for patients with sickle cell disease but are not specific to this population.[9]

These divergent recommendations are potentially contributory to substantial differences in practice across sickle cell centers; of note, practice at our institution is generally to continue antimicrobial prophylaxis in most patients.[10] The objective of this study was to describe our institution's incidence of IPD in patients who continued antimicrobial prophylaxis beyond age 5 years as compared with those whose antimicrobial prophylaxis was discontinued. Our secondary objectives were to describe the incidence of positive cultures (any organism from any source) in patients who continued antimicrobial prophylaxis as compared with those whose antimicrobial prophylaxis was discontinued, as well as the age at which antimicrobial prophylaxis was discontinued.

Materials and Methods

This was a single-center, retrospective, comparative cohort study conducted at a large, academic, freestanding children's hospital in the northeastern United States. Our comprehensive SCD center is an interdisciplinary clinic that manages almost a thousand children, adolescents, and young adults with SCD across a large metropolitan area.

Patients with SCD were identified by using ICD-9[11] and/or ICD-10[12] codes and were included if they were between the ages of 5 and 18 years during the study period (January 1, 2010–December 31, 2020) and did not have an episode of IPD or a history of splenectomy prior to age 5 years. Billing codes used for subject screening are listed in the Supplemental Table. Patients who received initial antimicrobial prophylaxis with an antibiotic other than penicillin were also excluded. Demographic data included age, sex, race and ethnicity, and immunization status (receipt of any doses of PCV-7, PCV-13, or PPSV-23 as documented during inpatient admission). Patient electronic medical records were reviewed for penicillin antimicrobial prophylaxis prescriptions (250 mg by mouth twice daily), including discontinuation dates if applicable, and cultures from any source. Patient records were reviewed from age 5 years until age 18 years, or the end of the study period, whichever came sooner. Cultures positive for *S pneumoniae* were reviewed for antibiotic resistance, if available. For the purposes of the primary outcome, repeated positive cultures were only counted as a single instance of IPD. Data were analyzed with measures of central tendency reported as mean ± SD for continuous data or counts and percentages for categorical data.

Results

A total of 617 patients were included for analysis (Supplemental Figure S1 for subject screening). Most patients had hemoglobin SS disease (n = 414, 67%) and were Black (n = 585, 95%). Receipt of any pneumococcal immunizations (PCV-7 or -13 or PPSV-23) was documented in 87% of patients (n = 537). Full patient demographics are presented in Table 1.

Sixty-five percent of patients (n = 399) remained on antimicrobial prophylaxis beyond age 18 years or at the end of the study period, with the remaining 218 patients' antimicrobial prophylaxis being discontinued at a mean age of 11.98 ± 4.21 years. Continuation of prophylaxis by genotype is presented in Supplemental Figure S2; a higher percentage of patients with more

Downloaded from http://meridian.allenpress.com/jppt/article-pdf/28/6/519/3288872/i2331-348x-28-6-519.pdf by guest on 22 February 2024

Table 1. Subject Demographics

	N = 617
Sex, n (%)	
Female	314 (51)
Race, n (%)	
Black	585 (95)
All other races	32 (5)
Ethnicity, n (%)	
Non-Hispanic	586 (95)
Hispanic or Latino	18 (3)
Did not disclose	13 (2)
Genotype, n (%)	
SS	414 (67)
SC	147 (24)
SB+	39 (6)
SB0	14 (2)
Unknown	3 (<1)
On prophylaxis beyond age 18 yr or at end of study period, n (%)	399 (65)
Age of discontinuation, mean ± SD, yr	11.98 ± 4.21

SB+, hemoglobin S beta-plus disease; SB0, SB0, hemoglobin S beta-zero disease; SC, SC, hemoglobin SC disease; SS, hemoglobin SS disease.

Table 2. Positive Cultures by Site and Organism

	Patients On Antimicrobial Prophylaxis n = 399	Patients Off Antimicrobial Prophylaxis n = 218
Patients with a positive culture, n (%)	84 (21)	39 (18)
Positive cultures, n	114	56
Urine culture	n = 54	n = 35
Escherichia coli	17	15
Normal/mixed flora	14	9
Non-speciated Gram-positive organisms	13	N/A
Others	10	11
Blood culture	n = 16	n = 18
Staphylococcus spp	5	5
Streptococcus spp (not *S pneumoniae*)	2	3
Escherichia coli	1	2
S pneumoniae	1	N/A
Others	7	8

N/A, not applicable

severe genotypes (SS [hemoglobin SS disease] and SB0 [hemoglobin S beta-zero disease]) continued antimicrobial prophylaxis. Of those patients whose antimicrobial prophylaxis was discontinued, annual rates of de-prescribing ranged from 6% to 13% of patients over the 10-year study period.

A total of 5267 cultures were reviewed from all body fluid and tissue sites. Only 1 patient was found to have IPD, presenting as *S pneumoniae* bacteremia that was positive in 2 of 2 blood cultures. This patient, a 13-year-old female with hemoglobin SS disease, was on antimicrobial prophylaxis at the time of infection. She experienced cardiac arrest and following return of spontaneous circulation, died secondary to septic shock leading to multisystem organ failure. This patient had completed a PCV-13 series and had received 2 doses of PPSV-23, administered 3 years apart (as compared with recommended 5-year interval between doses). The isolated pathogen was not serotyped, and thus resistance testing was not completed. This amounts to a 0.025% incidence of IPD in patients who continued antimicrobial prophylaxis (1/399); no patients whose antimicrobial prophylaxis was discontinued developed IPD.

After repeated results were excluded, a total of 160 cultures were positive. The rate of positive non-pneumococcal cultures was similar between both groups: 21% of patients receiving antimicrobial prophylaxis had a positive culture (114 cultures across 84 patients), compared with 18% of patients without antimicrobial prophylaxis (56 cultures across 39 patients). Culture data are presented by site and by pathogen in Table 2.

Discussion

Our findings show that antimicrobial prophylaxis is continued beyond age 5 years in most patients with SCD at our institution. IPD rarely occurs in patients, regardless of antimicrobial prophylaxis. The similar incidence of IPD in our study population (1 case of IPD in 399 patients on antimicrobial prophylaxis, with no cases in 218 patients off antimicrobial prophylaxis) and the study population in PROPS-II (2 cases of IPD in 200 patients on antimicrobial prophylaxis and 4 cases in 200 patients off antimicrobial prophylaxis) appears to support discontinuation of antimicrobial prophylaxis in patients who are not at increased risk of IPD at age 5 years (e.g., those with complete pneumococcal immunization and without a history of IPD).[6,7] Of note, PROPS-II[7] only included patients with hemoglobin SS and hemoglobin SB0 disease, whereas our study included patients from all SCD genotypes. Reassuringly, available data suggest a low incidence of IPD in the post-vaccine era, which we expect also contributed to our population having an overall lower rate of IPD relative to previous studies.[4] Findings of non-pneumococcal positive cultures were similar between groups; resistance was not specifically evaluated, but penicillin does not confer intrinsic activity against many of the pathogens detected, therefore effects were likely minimal. Based on these data, continued antimicrobial prophylaxis with penicillin does not appear to affect non-pneumococcal infections.

The annual number of patients whose prophylaxis was discontinued did not appear to increase over the

Downloaded from http://meridian.allenpress.com/jppt/article-pdf/28/6/519/3288872/i2331-348x-28-6-519.pdf by guest on 22 February 2024

course of the study period (annually, a range of 14 to 28 patients' antimicrobial prophylaxis was discontinued from 2011–2020). In consultation with hematologists at our institution, continuation of antimicrobial prophylaxis is discussed with all patients who are appropriate for discontinuation per the National Heart, Lung, and Blood Institute guidelines (age greater than 5 years, fully immunized without a history of IPD or surgical splenectomy)[8]. Practice at our institution is generally more conservative than guideline recommendations, with antimicrobial prophylaxis being continued in most patients and most frequently continued in patients with more severe genotypes (SS and SB0). This is congruent with a previously published survey of hematologists practicing in the United States, which demonstrated that approximately 25% continue prophylaxis in all patients, citing benefit of ongoing use outweighing the risk of adverse drug reaction or antibiotic resistance.[10] In our study, in patients whose antimicrobial prophylaxis is continued beyond age 5 years, discontinuation often occurs just before age 12 years following shared decision-making discussions with families. We expected to see rates of discontinuation proportionally increase with the proliferation of pneumococcal immunization, but this was not borne out by our findings. With further uptake of pneumococcal immunization and additional data, such as this study, that suggest antimicrobial prophylaxis can safely be de-prescribed, we expect to see discontinuation of antimicrobial prophylaxis to increase.

This study is not without limitations. There are multiple SCD centers in the metropolitan area, and the single-center design cannot completely reflect the management of the region-wide sickle cell population. Similarly, patients included in our study population may have received treatment for infectious complications at neighboring institutions, which our dataset does not include. Cultures are not typically collected for acute chest syndrome, a common infectious complication of SCD. Notably, the PROPS[6] and PROPS-II[7] trials did not include acute chest syndrome in their definition of IPD, so we do not expect that our overall incidence of IPD was affected. *Streptococcus pneumoniae* is rarely a documented cause of acute chest syndrome (<5%) and other common causative pathogens (*Mycoplasma* and *Chlamydia* spp) are not covered by penicillin and thus, penicillin is not likely to affect the incidence of acute chest syndrome.[13] To mirror the intervention studied by PROPS[6] and PROPS-II,[7] we only included antimicrobial prophylaxis with penicillin, which excluded several hundred patients. Expanding future studies to include prophylaxis with other antibiotics would be useful both in evaluating the incidence of IPD and in appraising the effects of chronic use of comparatively broader spectrum agents (e.g., amoxicillin, erythromycin) on selection for resistant pathogens.

Only immunizations that were documented during an inpatient encounter were included in our dataset; thus, immunization records for patients who did not have inpatient encounters are potentially incomplete. Had outpatient immunization records, as well as those from other institutions, been included, we expect that immunization rates would have been higher, because our physician colleagues routinely advocate for vaccinations during inpatient and outpatient visits. The "any" versus "none" paradigm used for reporting immunization status also includes patients who are incompletely immunized and at higher risk of infection.

Medication adherence, reason for discontinuation, and other comorbid medical problems were not addressed as part of this study. Future studies incorporating these whole-patient considerations and their effects on medication adherence, as well as the pharmacist's role in addressing barriers to adherence, are needed to evaluate the role of antimicrobial prophylaxis more comprehensively in patients with SCD. Rates of adverse drug reactions (poor taste, gastrointestinal discomfort, and allergic reaction, among others) to penicillin have been reported as low in previous studies on antimicrobial prophylaxis in SCD, but future studies should evaluate these effects owing to their potentially considerable effect on patient and family quality of life.[6,7] Finally, discrepancies between billing codes used in the usual course of patient care and those used for subject screening may have led to an unintended exclusion of patients from the study population.

Conclusion

The results found in this study support appropriate de-prescribing of antimicrobial prophylaxis in patients with SCD who are not at high risk for IPD. Further multicenter studies are needed to evaluate the effects of antimicrobial prophylaxis with alternative agents on antibiotic resistance, examine provider rationale for continuation of antimicrobial prophylaxis, and evaluate the quality of life effects (e.g., medication adherence and adverse drug reactions) of antimicrobial prophylaxis.

Article Information

Affiliations. Department of Pharmacy (TGE, RMK, JZ, AM), Children's Hospital of Philadelphia, Philadelphia, PA.

Correspondence. Tyler G. Eastep, PharmD; tg.eastep@live.com

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. This study was approved by the institution review board, and a waiver of consent was obtained.

Downloaded from http://meridian.allenpress.com/jppt/article-pdf/28/6/519/3288872/i2331-348x-28-6-519.pdf by guest on 22 February 2024

Acknowledgments. Results were presented as a platform presentation at the Pediatric Pharmacy Association Annual Meeting in Norfolk, VA, on May 5, 2022. Many, many thanks to the hematologists who contributed to this project, Drs Helge Hartung and Cynthia Norris, as well as our pharmacy colleague, Dr Alyssa Hager; their expertise and guidance were invaluable.

Submitted. November 9, 2022

Accepted. January 19, 2023

Copyright. Pediatric Pharmacy Association. All rights reserved. For permissions, email: membership@pediatricpharmacy.org

Supplemental Material. DOI: 10.5863/1551-6776-28.6.519.S1F
DOI: 10.5863/1551-6776-28.6.519.S2F
DOI: 10.5863/1551-6776-28.6.519.S1T

References

1. McCavit TL. Sickle cell disease [correction appears in *Pediatr Rev.* 2012;33(8):375 and *Pediatr Rev.* 2012;33(8):383]. *Pediatr Rev*. 2012;33(5):195–206.
2. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. *Int J Infect Dis*. 2010;14(1):e2–e12.
3. Payne AB, Link-Gelles R, Azonobi I, et al. Invasive pneumococcal disease among children with and without sickle cell disease in the United States, 1998 to 2009. *Pediatr Infect Dis J*. 2013;32(12):1308–1312.
4. Adamkiewicz T, Thomas S, Tunali A, et al. Population-based surveillance of pneumococcal infections in children with sickle cell disease before and after prevnar 7® and prevnar 13® licensure: implications for expanded vaccination. *Blood*. 2021;138(suppl 1):763.
5. Committee on Infectious Diseases. Recommended childhood and adolescent immunization schedule: United States, 2021. *Pediatrics*. 2021;147(3):e2020049775.
6. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia: arandomized trial. *N Engl J Med*. 1986;314(25):1593–1599.
7. Falletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia: Prophylactic Penicillin Study II. *J Pediatr*. 1995;127(5):685–690.
8. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members [correction appears in *JAMA*. 2014;312(18):1932 and *JAMA*. 2015;313(7):729]. *JAMA*. 2014;312(10):1033–1048.
9. Davies JM, Lewis MP, Wimperis J, et al. Review of guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen: prepared on behalf of the British Committee for Standards in Haematology by a working party of the Haemato-Oncology task force. *Br J Haematol*. 2011;155(3):308–317.
10. McCavit TL, Gilbert M, Buchanan GR. Prophylactic penicillin after 5 years of age in patients with sickle cell disease: a survey of sickle cell disease experts. *Pediatr Blood Cancer*. 2013;60(6):935–939.
11. World Health Organization. *International Classification of Diseases,Ninth Edition*. WHO; 1978.
12. World Health Organization. *International Classification of Diseases,Tenth Edition*. WHO; 2010.
13. Martí-Carvajal AJ, Conterno LO, Knight-Madden JM. Antibiotics for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev*. 2019;9(9):CD006110.

Downloaded from http://meridian.allenpress.com/jppt/article-pdf/28/6/519/3288872/i2331-348x-28-6-519.pdf by guest on 22 February 2024