Provision of Pneumococcal Prophylaxis for Publicly Insured Children With Sickle Cell Disease

Colin M. Sox, MD
William O. Cooper, MD, MPH
Thomas D. Koepsell, MD, MPH
David L. DiGiuseppe, MSc
Dimitri A. Christakis, MD, MPH

ACH YEAR IN THE UNITED STATES, approximately 2000 children are born with sickle cell disease (SCD).1 The incidence of invasive Streptococcus pneumoniae infection is 20- to 100-fold higher in children with SCD than in the general population.2,3 Penicillin prophylaxis for children with hemoglobin SS reduces the incidence of invasive pneumococcal infection by 84%, independent of pneumococcal immunization status.4 According to recent American Academy of Pediatrics (AAP) consensus statements, all children with hemoglobin SS and 5-ß° thalassemia should take daily antibiotics to provide pneumococcal prophylaxis from age 2 months, or the time of their diagnosis, through their fifth birthday.5,6

Achieving prophylaxis in children with SCD requires 2 steps: children must obtain antibiotics prescribed by a clinician, and they must take the medication as directed. The second step has been examined in several studies of patient adherence with penicillin prophylaxis using a variety of techniques. Parents have reported their children’s compliance to be 61% to 67%,7,9 and computerized pill bottles have measured 67% adherence with prophylaxis.10 However, urine testing, which detects penicillin taken in the prior 15 to 24 hours, has revealed compliance varying from 47% to 64%.8,9,11,12 These 6 studies were conducted at single institutions, included patients older than 5 years, and were subject to self-reporting bias or the artificiality of research conditions. Furthermore, to

Context It is recommended that children younger than 5 years with sickle cell disease (SCD) take daily prophylactic antibiotics to prevent pneumococcal infections; however, how much prophylactic medication they actually are dispensed is unclear.

Objectives To measure the amount of prophylactic antibiotics dispensed to young children with SCD and to investigate factors associated with increased delivery of medication.

Design, Setting, and Patients Retrospective longitudinal study conducted January 1995 through December 1999 using Tennessee and Washington State Medicaid administrative claims and encounter data. Children (N=261) who had 1 inpatient or 2 outpatient claims or encounters listing an International Classification of Diseases, Ninth Revision, Clinical Modification code for SCD, were younger than 4 years at study entry (mean age, 1.4 years), and were continuously enrolled in Medicaid for a 1-year period.

Main Outcome Measure Number of days during a 365-day period covered by prescription fills for a penicillin or macrolide antibiotic, or for trimethoprim-sulfamethoxazole.

Results In a 365-day period, patients were dispensed a mean of 148.4 (SD, 121.3; median, 114; interquartile range [IQR], 39-247) days of prophylactic medication. The total amount of medication dispensed varied widely: 10.3% of patients received none and 21.5% received more than 270 days of medication. In a 365-day period, a mean of 12.7 (SD, 10.5; range, 0-40) prophylactic prescriptions were filled per patient. The median prescription duration was 10 days. In a multivariate linear regression model adjusting for state, sex, age at study entry, inclusion year, residence in urban community, outpatient inclusion encounter, required prescription co-payment, and number of outpatient visits for nonpreventive care, each preventive visit was associated with 12.0 (95% confidence interval [CI], 2.3-21.7) additional days of prophylactic antibiotics, and each emergency department visit was associated with 10.0 (95% CI, 1.2-18.8) additional days.

Conclusions Publicly insured children with SCD may receive inadequate antibiotic prophylaxis against pneumococcal infections, placing them at increased risk of morbidity and mortality; however, increased numbers of outpatient visits for preventive care are associated with improved provision of prophylactic antibiotics.

JAMA. 2003;290:1057-1061

©2003 American Medical Association. All rights reserved.
date no population-based study has examined the amount of pneumococcal prophylactic medication dispensed to children with SCD. Dispensing prophylactic medication to this population is critical, as optimal compliance can only maximize the potential benefits of dispensed medication.

We sought to determine the amount of prophylactic medication dispensed to children younger than 5 years with SCD who were covered by TennCare and Washington State Medicaid. These programs fund care to large numbers of children and maintain data systems that capture nearly all prescriptions filled for their patients. We also investigated factors associated with increased receipt of prophylactic medication.

**METHODS**

**Data Source and Setting**

We analyzed administrative claim and encounter data from TennCare and Washington State Medicaid from 1995 to 1999. TennCare is Tennessee’s health insurance program for Medicaid enrollees and for uninsured or uninsurable individuals. TennCare is a managed care program, and Washington State Medicaid uses both fee-for-service and managed care plans. Medicaid and vital records data from both states have been used extensively to conduct health services research in children.

The Medicaid programs in Tennessee and Washington have similar regulations for maximum prescription length and refills. Like new prescriptions, renewals generate Medicaid claims in both states. Washington’s Medicaid program does not require co-payments for prescriptions, while TennCare patients whose eligibility is due to “uninsured or uninsurable” status are required to pay $5 per prescription. During the study’s time period, neither state made any significant changes to prescription regulation or to program reimbursement that would have impacted the use of prophylactic medication. All children born in Tennessee and Washington are screened at birth for hemoglobinopathies.

**Patients**

We included in our study population all children who were documented to have SCD between 1995 and 1998, were 1 to 48 months old when their study period began, and were continuously enrolled in Medicaid during their 365-day study period. As has been done previously, we identified children as having SCD if they had 1 inpatient or 2 outpatient claims or encounters that cited *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes for SCD in any diagnosis field. We define the “inclusion encounter” as the health care visit that generated the ICD-9-CM code for SCD that fulfilled our operational definition of SCD. We used the 4 ICD-9-CM codes for SCD (282.6, 282.60, 282.61, or 282.62) that specifically exclude sickle cell trait and hemoglobin SC, conditions for which prophylaxis is not absolutely indicated.

**Study Period**

During a 5-year period, children with SCD were identified and subsequently assessed for 365 days. The inclusion date for patients identified by a hospitalization was the discharge date, and for patients identified by 2 outpatient claims it was the date of their second outpatient encounter. Children’s study periods began on their inclusion date and ended 365 days later. Continuous enrollment during the 365-day study period was defined as having no gaps in enrollment longer than 30 days, to allow for adequate measurement of health service utilization during the study period. While patients’ 365-day study periods may have occurred over different calendar years, there were no changes from 1995 to 1999 in guidelines for pneumococcal prophylaxis.

**Outcome Measure**

To calculate the amount of prophylactic antibiotics dispensed to children during their study periods, we used the days provided by each unique prescription fill of an oral antibiotic to which pneumococcus is sensitive. To identify prophylactic prescription fills, we used the claim and encounter records for all prescription fills for any medication in the penicillin and macrolide drug classes, as well as for trimethoprim-sulfamethoxazole. While penicillin is the drug of choice for pneumococcal prophylaxis, we included macrolides because erythromycin is recommended in the case of penicillin allergy.

While trimethoprim-sulfamethoxazole is not specifically recommended for pneumococcal prophylaxis in SCD, we also classified it as a prophylactic medication because it is used for prophylaxis in other situations (eg, *Pneumocystis jiroveci* prophylaxis for children with human immunodeficiency virus), and because *S pneumoniae* is sensitive to it. Claims data did not allow us to measure medication samples.

We included all medications in both the penicillin and macrolide drug classes, as opposed to only examining penicillin and erythromycin specifically, because they all can provide prophylaxis against *S pneumoniae*. Some physicians may prescribe other medications in these classes (eg, amoxicillin) for prophylaxis due to convenience or patient preferences. We included all prescription fills regardless of their indication. We recognize that this approach could include prescriptions written for both prophylactic and therapeutic indications; for example, antibiotics prescribed for acute conditions unrelated to SCD (eg, otitis media) would still be counted. The Medicaid claims data did not identify either the setting in which prescriptions were written or their indication. Choosing to classify medications as “prophylactic” without knowing their indication tends to overestimate the medication intended for prophylaxis. However, it would provide a clinically important measure: the amount of medication that provides systemic prophylaxis.

We included the number of days covered by all prescriptions (maximum, 365 days) even when the fill date of a prescription occurred within the period covered by a preceding prescription, as we assumed that patients would stockpile surplus medication for use at a later date. This approach is conservative because it might tend to overestimate the amount of medication available to children.
alternative would have been to assume that each new prescription was filled, leftover medication was discarded or lost. To test the strength of our assumption, we also conducted analyses with prophylaxis days calculated using the alternative assumption. Prior studies of prophylaxis in adults have handled this issue both ways.21,22

**Predictor Variables**

We collected information from the administrative data sets on each child’s sex, age, state, community type (urban or nonurban), inclusion year, requirement for prescription co-payment, and health care utilization. We calculated children’s age in days on their inclusion date. Children’s study periods began on their inclusion date and ended 365 days later. Because children entered our study only after significant interaction with the health care system, we expected the age at study entry to be relatively old. We used children’s home ZIP codes to classify their community type using the 1990 Rural Urban Commuting Areas (RUCA) codes. The RUCA codes combine the standard Bureau of Census area definitions with commuting information to characterize the rural/urban status of the nation’s Census tracts.23 We classified RUCA codes 1 through 3 as urban communities and codes 4 through 10 as nonurban communities. We defined preventive visits as those using at least 1 preventive Current Procedural Terminology code (V03-06, V20-21, V68.1, V70, V78.1), and defined nonpreventive visits as all other outpatient visits with physicians that did not occur in an emergency department. During each child’s 365-day study period, we counted the number of unique emergency department visits, preventive and nonpreventive clinic visits, and hospitalizations. When separate claims or encounters for different types of visit occurred on the same date, we counted each type of visit individually.

**Analysis**

We present means for continuous variables (days of prophylactic antibiotics, age in days, and number of visits) frequencies and percentages for categorical variables (sex, age categories, community type, inclusion year, type of inclusion encounter, and required prescription co-payment). We used age measured in days to enhance precision. To make bivariate comparisons between prophylaxis days and predictor variables, we used least-squares regression. Multivariate linear regression was used to assess predictors of the number of days of prophylactic antibiotics dispensed in a 365-day period. We used robust SEs to account for clustering by child’s ZIP code. All variables hypothesized a priori to potentially affect receipt of prophylaxis were included in the regression models: age, inclusion year, sex, community type, state, type of inclusion encounter, required prescription co-payment, and number of emergency department, preventive, and nonpreventive outpatient visits. We used the likelihood-ratio test to test for interactions between the inclusion encounter type and the health care utilization variables on the provision of prophylaxis. The estimated β coefficients are provided for each predictor variable, which can be interpreted as the difference in the days of prophylactic antibiotics dispensed between 2 groups differing by 1 unit in each covariate. All statistical analyses were performed using Stata 8.0 (Stata Corporation, College Station, Tex).

The human subjects divisions of the TennCare Bureau, the Vanderbilt University institutional review board, the Washington State institutional review board, and the department of public health in Tennessee approved this study.

**RESULTS**

A total of 261 children were included in the study. Children’s mean age at study entry was 1.4 years (median, 0.9 years; range, 1 month to 3.9 years). During their 365-day period, 64% of the children were hospitalized at least once. Patients mostly lived in urban communities and had many nonpreventive visits during the 365-day study period (Table 1).

Overall, a mean of 148.4 days (41% of the 365-day study period) of prophylactic antibiotics was dispensed during the study year (SD, 121.3; median, 114; interquartile range, 39-247). The amount of prophylactic medication dispensed varied: 10.3% of children received none, and 21.5% received more than 270 days of medication (FIGURE). Prescription length and the number of prescriptions filled also varied. The median duration of individual prescriptions was 10 days (interquartile range, 10-14 days). During the 365-day study period, a mean of 12.7 prophylactic prescriptions were filled per patient (SD, 10.5; range, 0-40), of which 12.1 were for a penicillin antibiotic (SD, 10.3; range, 0-39), 0.4 were for a macrolide antibiotic (SD, 0.8; range, 0-9), and 0.2 were for trimethoprim-sulfamethoxazole (SD, 0.5; range, 0-4).

©2003 American Medical Association. All rights reserved.
In bivariate analyses, statistically significant associations were found between the amount of prophylactic antibiotics dispensed and the number of emergency department visits, preventive outpatient visits, and nonpreventive outpatient visits (Table 2). In a multivariate linear regression model controlling simultaneously for state, sex, age at inclusion date, inclusion year, residence in urban community, outpatient inclusion encounter, required prescription co-payment, and number of outpatient visits for nonpreventive care, the number of preventive visits and emergency department visits both were significantly associated with increased provision of prophylactic antibiotics (Table 2). Specifically, each visit for preventive care was associated with 12.0 (95% confidence interval [CI], 2.3-21.7) additional days of prophylactic medication dispensed, and each emergency department visit was associated with 10.0 (95% CI, 1.2-18.8) additional days. Of the potential interactions we tested, none was statistically significant.

To test the strength of our assumption that children saved surplus medication due to overlapping prescriptions, we repeated our analyses assuming that surplus medication was discarded. Using this definition, a mean of 136.2 (SD, 109.4; median, 114; interquartile range, 38-227) days of prophylactic medication (37% of the study year) was dispensed during the 365-day study period. Using a multivariate linear regression model controlling for the same variables as the regression shown in Table 2, each preventive visit was associated with 10.8 (95% CI, 2.0-19.6) additional days of prophylactic medication dispensed and each emergency department visit was associated with 8.7 (95% CI, 0.8-16.6) additional days.

**COMMENT**

Children younger than 5 years with SCD and covered by Medicaid in Tennessee and Washington State only received, on average, enough prophylactic antibiotics to cover about 40% of the year-long study period. Evidence-based guidelines recommend that these children should take daily medication for pneumococcal prophylaxis. Because we measured the provision of prophylactic medication from a pharmacy, not necessarily the amount of medication consumed, this estimate can be interpreted as a best-case scenario for the number of days of prophylaxis achieved. Additionally, we found that preventive outpatient visits were associated with a statistically and clinically significant improvement in provision of prophylactic medication. Our work is the first population-based analysis of the delivery of antibiotics that provide prophylaxis against *S. pneumoniae* to young children with SCD. Pneumococcal prophylaxis for children with SCD is an understudied preventive measure whose effectiveness has been clearly demonstrated in a randomized trial.

Our findings extend the limited existing literature on adherence to pneumococcal prophylaxis for children with SCD. It is possible that the previous reports of poor compliance were due to a combination of poor provision of medication to patients and their poor adherence to taking the medication. We found that children were dispensed 40% of the recommended amount of prophylactic medication, and compliance literature suggests that these children probably were appropriately protected against pneumococcal infections for less than 40% of the year. Reasons for such poor provision of prophylactic medication are unknown, but may include physicians not writing prescriptions for prophylactic antibiotics or patients not taking written prescriptions to the pharmacy. Notably, children frequently interacted with the health care system, with a mean of 13 outpatient encounters per year, suggesting ample missed opportunities to emphasize and assess compliance with prophylaxis.

Our study supports other work demonstrating that quality of health care is affected by patients' insurance and socioeconomic status. For example, only 36% of children with SCD who received Supplemental Security Income and were covered by Medicaid had at least 1 visit with a relevant subspecialist in 1 year. Similarly, public insurance was found in 1 study to be a risk factor for poor adherence to penicillin prophylaxis for children with SCD. Health care utilization for children with SCD has been directly linked to their families' socioeconomic status and to the distance between their home and the clinic.

We measured the delivery of antibiotics that provide prophylaxis against pneumococcus to children with SCD, regardless of the intent of the prescribing physician. For example, a child who received 3 prescriptions for amoxicillin to treat 3 separate occurrences of otitis media for...
10 days each was classified as receiving the same amount of prophylactic medication as a child who received a single 30-day prescription for penicillin intended for prophylaxis. Although one might assume that prescriptions intended for prophylaxis are typically written for either 15 or 30 days depending on the antibiotic formulation, our study’s median prescription length was 10 days. This short median prescription length suggests that the indication for the majority of filled prescriptions may have been therapeutic. Because we did not have data on the indications for the filled prescriptions, we could not test this hypothesis.

Several limitations to this study warrant comment. First, because we used an administrative database of insurance claims and encounters, it is possible that not all prescription fills or encounters were captured. However, in both states pharmacies must submit claims in order to be reimbursed, making it unlikely that many claims were missed, and prescription claims data have been validated as a reliable outcome.23,26 Second, our study included all eligible patients covered by TennCare and Washington State Medicaid, and may not be generalizable to other populations. However, most specialty care for children with SCD in Tennessee and Washington State occurs in tertiary care centers located in urban areas, as it does in most states. The proportion of our patients who lived in urban areas was virtually identical to the proportion reported by a recent study of children with SCD covered by Medicaid living in 4 states.19 Third, we could not measure the number of antibiotic samples dispensed to patients free of charge, but this practice is probably not common because most prophylactic antibiotics are available as generic equivalents. Lastly, we could not measure the number of appropriate prescriptions that were written but not taken to a pharmacy, the number of unsuccessful attempts to fill prescriptions, or the patients’ actual medicine-consuming behavior. However, we measured a clinically meaningful outcome—the amount of prophylactic antibiotics dispensed to children who should receive prophylaxis. Our finding that these children were dispensed so little prophylactic medication is a reason for concern.

This study has important clinical implications. First, the provision of prophylactic medication to young children with SCD may be poor and not in compliance with current guidelines, placing many children at significantly increased risk of major morbidity and mortality. Second, interventions to improve the provision of prophylaxis to this population are clearly warranted. We found that more preventive visits were associated with improved provision of prophylaxis, which suggests one possible approach. A systems perspective for management of chronic disease has been very successful in adult patients,27 suggesting that components of the chronic care model28 should be tested in this vulnerable pediatric population.

Author Contributions: Study concept and design: Sox, Cooper, Christakis. Acquisition of data: Sox, Cooper, Christakis. Analysis and interpretation of data: critical revision of the manuscript for important intellectual content: Sox, Cooper, Koepsell, DiGiuseppe, Christakis. Drafting of the manuscript: Administrative, technical, or material support: Sox, Christakis. Statistical expertise: Sox, Cooper, Koepsell, Christakis. Obtained funding: Cooper, Christakis. Study supervision: Christakis. Funding/Support: This study was supported in part by the Nesholm Family Foundation (Seattle, Wash). Drs Christakis and Cooper are supported by the Robert Wood Johnson Generalist Physician Faculty Scholar program.

Disclaimer: The opinions expressed herein are those of the authors and do not necessarily represent the views of the Robert Wood Johnson Foundation.

Acknowledgment: We acknowledge the helpful feedback received on the manuscript from Salbach MD, Fred Rivara, MD, MPH, and Hal Sox, MD. This work was conducted while Colin Sox was a Robert Wood Johnson Clinical Scholar at the University of Washington, Seattle, and he would like to acknowledge the program’s work-in-progress seminar.

REFERENCES


