Compliance With Penicillin Prophylaxis in Patients With Sickle Cell Disease

Stephen J. Teach, MD, MPH; Kathleen A. Lillis, MD; Mauro Grossi, MD

Objective: To assess factors related to compliance with penicillin prophylaxis among patients with sickle cell disease.

Design: Prospective case series.

Setting: Urban pediatric medical center where universal penicillin prophylaxis is recommended for all patients with any sickle cell hemoglobinopathy independent of age.

Participants: Eligible patients with sickle cell hemoglobinopathies were enrolled in either the emergency department or the sickle cell clinic.

Main Outcome Measures: Compliance was assessed by structured interview and by urine assay with an established method (Micrococcus luteus with disk diffusion) that detects excreted penicillin up to 15 hours after each dose administration.

Results: Of the 159 patients actively followed up at the sickle cell center, 123 (77.3%) eligible patients were enrolled. Reported compliance by structured interview (≥1 dose of penicillin V potassium within 15 hours of enrollment) was 83 of 123 patients (67.5%; 95% confidence interval, 59.2%-75.8%), whereas measured compliance as determined by urine assay was 53 of 123 patients (43.1%; 95% confidence interval, 31.3%-51.7%). Measured compliance was significantly greater in patients younger than 5 years than in those older than 5 years (25/41 [61%] vs 28/82 [34%], respectively; P = .004), and was significantly greater in patients with private insurance than in those with public insurance (17/28 [61%] vs 33/90 [37%], respectively; P = .02). Measured compliance was not significantly associated with sex, site of recruitment, hemoglobinopathy, or chief complaint in the emergency department.

Conclusions: Measured compliance was poor, and patients and/or their families frequently misrepresented their compliance when interviewed. These data suggest that efforts are necessary to improve overall compliance, and they identify groups at greatest risk for noncompliance.


I NFANTS and young children with sickle cell disease have long been known to be susceptible to bacteremia and meningitis due to Streptococcus pneumoniae. Daily penicillin prophylaxis decreases episodes of pneumococcal bacteremia in patients with sickle cell disease younger than 5 years of age. Current recommendations are to institute prophylaxis as soon as the diagnosis of sickle cell disease is established (preferably by 2 months of age) and to continue it at least through age 5 years. Prophylaxis after age 5 years is optional, but is recommended in children with prior episodes of severe pneumococcal infection or splenectomy and in those not receiving comprehensive care.

Because the Sickle Cell Center at the Children's Hospital of Buffalo, Buffalo, NY, recommends continued penicillin prophylaxis for all patients regardless of age or underlying sickle cell hemoglobinopathy, it provides an ideal setting to examine factors related to compliance with prophylaxis in a group of patients receiving comprehensive care for sickle cell disease.

RESULTS

DEMOGRAPHICS

During the 10-month study period, the sickle cell clinic actively followed up 159 patients with documented sickle cell hemoglobinopathy. Of these, 125 patients...
PATIENTS AND METHODS

We prospectively obtained a convenience sample of patients with sickle cell disease who presented to either the emergency department or the sickle cell clinic at the Children’s Hospital of Buffalo during the 10-month study period (April 1996 through January 1997). An unselected subset of patients were enrolled more than once. It was the policy of the Sickle Cell Center at the Children’s Hospital of Buffalo for at least 5 years before the start of the study and for the entire duration of the study that all patients with a sickle cell hemoglobinopathy receive penicillin V potassium prophylaxis in a dose of 125 mg twice daily prior to age 2 years and 250 mg twice daily after 2 years of age. Review of prophylaxis was a standard part of each clinic visit at all ages. The sickle cell clinic at Children’s Hospital of Buffalo receives referrals from newborn screening and schedules patient visits every 2 months from birth to 6 months of age, every 3 months from 6 months to 2 years of age, and every 6 months from 2 years of age onward.

Patients were eligible for enrollment if they had a documented sickle cell hemoglobinopathy (homozygous hemoglobin SS [HbSS], heterozygous hemoglobin SC [HbSC], heterozygous hemoglobin S β-thalassemia [HbSβthal], or HbSS with high (>20%) persistent fetal hemoglobin [HbP]) and if they were actively followed up in the sickle cell clinic at the Children’s Hospital of Buffalo (≥1 clinic visit in the preceding year). Patients were excluded if they had consumed antibiotics other than their penicillin prophylaxis in the 72 hours prior to enrollment or if they had a history of penicillin allergy.

After informed consent was obtained, each patient was asked to provide a urine sample, which was immediately refrigerated at 4°C. Catheterized or bagged specimens were obtained when the patient failed to void spontaneously. Each urine sample was assayed by an established method (Micrococcus luteus with disk diffusion) that detects excreted penicillin up to 15 hours after each dose administration. Compliance was defined as evidence of any zone of inhibited bacterial growth around the disk.

In addition, a structured interview was performed at enrollment in which patients and/or their family were questioned about their recent compliance with penicillin prophylaxis. Additional demographic information was abstracted from the patients’ medical records, including age, sex, insurance status, and diagnostic code at discharge from the emergency department.

Categorical variables were assessed by chi-squared analysis, and continuous variables were assessed by the Student t test. Statistical analysis was performed with the Statistical Program for the Social Sciences (SPSS Inc, Chicago, Ill). Significance was defined as P<.05.

This study was approved by the institutional review board of the Children’s Hospital of Buffalo.

were enrolled in the study. Two were subsequently excluded (1 because the urine specimen was mishandled and 1 because of a penicillin allergy), leaving 123 (77.3%) eligible patients for analysis. These patients are described in Table 1. The mean±SD age of the patients was 9.0±6.1 years (range, 0.3-24.2 years), which was significantly younger than that of the group of patients who were not enrolled or were excluded (12.5±5.9 years; P=.003). There were no significant differences between the 2 groups with regard to sex, underlying hemoglobinopathy, or insurance status. There were no significant differences between the patients enrolled in the clinic and those enrolled in the emergency department with regard to age, sex, underlying hemoglobinopathy, or insurance status.

COMPLIANCE

Overall, 53 of 123 patients (43.1%; 95% confidence interval, 31.3%-51.7%) were compliant with their penicillin prophylaxis at their first enrollment in the study (ie, their urine specimens yielded zones of inhibition with the M luteus assay). By comparison, 83 of 123 patients (67.5%; 95% confidence interval, 59.2%-75.8%) reported consuming 1 dose of penicillin within the prior 15 hours. Patients who reported taking 1 dose of penicillin within the prior 15 hours were significantly more likely to have penicillin in their urine than those who reported taking no doses of penicillin within the prior 15 hours (49/83 [59%] vs 3/39 [8%], respectively; P<.001). One patient was unsure if he had taken a dose within 15 hours of enrollment.

The mean±SD number of patients with measured compliance at initial enrollment were significantly younger than patients with measured noncompliance

Table 1. Demographics of Eligible Patients (N=123)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>61 (49.6)</td>
</tr>
<tr>
<td>Female</td>
<td>62 (50.4)</td>
</tr>
<tr>
<td>Recruitment site</td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>74 (60.2)</td>
</tr>
<tr>
<td>Emergency department</td>
<td>49 (39.8)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Clinic visit for routine care</td>
<td>74 (60.2)</td>
</tr>
<tr>
<td>VOC</td>
<td>23 (18.7)</td>
</tr>
<tr>
<td>Fever</td>
<td>18 (14.6)</td>
</tr>
<tr>
<td>Fever and VOC</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (4.1)</td>
</tr>
<tr>
<td>Insurance status</td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>90 (73.2)</td>
</tr>
<tr>
<td>Private</td>
<td>28 (22.8)</td>
</tr>
<tr>
<td>None</td>
<td>5 (4.1)</td>
</tr>
<tr>
<td>Hemoglobinopathy</td>
<td></td>
</tr>
<tr>
<td>HbSS</td>
<td>60 (48.8)</td>
</tr>
<tr>
<td>HbSC</td>
<td>31 (25.2)</td>
</tr>
<tr>
<td>HbSβthal</td>
<td>16 (13.0)</td>
</tr>
<tr>
<td>HbSS-HPFH†</td>
<td>13 (10.6)</td>
</tr>
<tr>
<td>Indeterminate‡</td>
<td>3 (2.4)</td>
</tr>
</tbody>
</table>

*VOC indicates vaso-occlusive crisis; HbSS, homozygous hemoglobin SS; HbSC, heterozygous hemoglobin SC; HbSβthal, heterozygous hemoglobin S β-thalassemia; and HPFH, high persistent fetal hemoglobin.
†HbSS with high (>20%) persistent fetal hemoglobin.
‡Infants younger than 6 months with high (>80%) fetal hemoglobin and no hemoglobin A.
During the 10-month study period, there were 2 episodes of documented pneumococcal bacteremia among the 159 patients actively followed up in the sickle cell clinic. One episode occurred in a 16-year-old boy whose initial urine specimen contained no penicillin. The other episode occurred in a 10-month-old male infant whose mother admitted to not providing penicillin prophylaxis. Urine collected from this patient 3 weeks later demonstrated the presence of penicillin. These 2 episodes yield a rate of 2.9 episodes of bacteremia per 100 patient-years of observation overall, and a rate of 2.9 episodes of bacteremia per 100 patient-years of observation for those younger than 5 years of age.

**COMMENT**

Despite the structured clinic setting in which the group of patients in our study were managed, fewer than half (43.1%) were compliant with their recommended penicillin prophylaxis at the time of their initial enrollment. Because penicillin prophylaxis provides no immediate tangible benefits for patients with sickle cell disease, it provides little positive reinforcement for strict compliance. Yet noncompliance with any medical regimen with proven clinical efficacy puts patients at risk for poor outcome. In our study, both episodes of pneumococcal bacteremia occurred in patients with measured noncompliance.

Noncompliance is a pervasive problem in several other chronic pediatric conditions. Although measurements of compliance differ in each case, prior studies have documented levels of noncompliance with long-term medical regimens of 10% to 60% in pediatric patients with end-stage renal disease, chronic asthma, diabetes, tuberculosis, and cancer. Given the experience with these chronic medical conditions, it is not surprising that compliance with penicillin prophylaxis in our population was so low.

Three smaller studies of compliance with prophylaxis in patients with sickle cell disease yielded overall compliance results similar to ours. Pegelow et al examined compliance in 20 patients using the *M lutea* disk diffusion method and found that 11 (55%) were compliant. Also using the *M lutea* method, Buchanan et al reported compliance in an unselected subgroup of 51 patients (41.5%) was enrolled more than 1 time in the study (at distinct presentations to either the clinic or emergency department) and provided a total of 141 urine specimens (median, 2 specimens; range, 2-8 specimens). Of the patients who tested positive for penicillin in their urine at their initial enrollment, 15 (79.0%) tested negative on 1 or more subsequent urine specimens. Of the 32 patients whose urine specimen tested negative for penicillin at their initial enrollment, 21 (65.6%) tested negative on all subsequent urine specimens. One 17-year-old girl tested negative on 7 consecutive specimens over an 8-month period.

**BACTEREMIA**

During the 10-month study period, there were 2 episodes of documented pneumococcal bacteremia among the 159 patients actively followed up in the sickle cell clinic. One episode occurred in a 16-year-old boy whose initial urine specimen contained no penicillin. The other episode occurred in a 10-month-old male infant whose mother admitted to not providing penicillin prophylaxis. Urine collected from this patient 3 weeks later demonstrated the presence of penicillin. These 2 episodes yield an adjusted rate for the 10-month period of the study of 1.5 episodes of bacteremia per 100 patient-years of observation overall, and a rate of 2.9 episodes of bacteremia per 100 patient-years of observation overall, and a rate of 2.9 episodes of bacteremia per 100 patient-years of observation for those younger than 5 years of age.
collected multiple specimens from 37 patients and found that 87 (64.4%) of 135 contained penicillin. Using a slightly different urine assay, Cummins et al20 reported penicillin in 10 (44%) of 23 urine specimens tested. As in our study, they noted a striking disparity between reported compliance (62%) and actual measured compliance (44%). Our study is superior to each of these prior efforts because we studied a larger group of patients and extended the analysis by identifying subgroups with high and low compliance.

One group with significantly greater compliance was patients younger than 5 years. Because these patients are at highest risk for bacteremia, they therefore have the most to benefit from prophylaxis. Compliance may be higher in this age group because patients younger than 5 years receive their prophylaxis from their parents as opposed to taking it themselves. Alternatively, staff in the clinic may emphasize compliance more strongly in younger patients because of their known higher risk for bacteremia.

New education efforts in the clinic setting may help parents understand that compliance may decrease as they begin to rely on their children to take their own medication. If the practitioner decides to continue penicillin prophylaxis beyond 5 years of age, supervised dispensing of the drug by parents should be recommended for as long as possible. In addition, the practitioner should counsel both the family and the older child on the importance of continued compliance.

We also identified public insurance as a risk factor for noncompliance. The reasons are unclear. Patients were seen routinely in the clinic and the emergency department without regard to their insurance status. There were neither different facilities nor different approaches to care for patients with public insurance. In New York State, prescriptions for penicillin are covered by Medicaid for periods up to 6 months (in 1-month renewal aliquots). Private insurers are more restrictive, often requiring special exemption letters from physicians to allow long-term medications. Thus, restricted access does not explain the noncompliance among the public insurance sector. Last, we have no evidence that patients receiving public insurance were older, attended the clinic less frequently, or were less educated or otherwise less able to understand the importance of compliance.

Our data are limited because, for the majority of patients, we only measured compliance at one point in time. We did assess compliance longitudinally in the unslected subgroup of 31 patients who provided more than 1 urine specimen at distinct times. Most of the patients whose specimens tested negative initially had subsequent specimens that tested negative (21/32 [66%]), and most of the patients whose specimens tested positive initially had 1 subsequent negative specimen (13/19 [79%]). In other words, patients who were noncompliant at enrollment tended to remain noncompliant, and patients who were compliant at enrollment were often subsequently noncompliant.

The poor compliance in our population raises the question of why the incidence of pneumococcal bacteremia was so low. Although the rate of pneumococcal bacteremia in our study for patients younger than 5 years, 2.9 episodes per 100 patient-years, was higher than the rate in the intervention group (patients <4 years of age) of the Prophylactic Penicillin Study (PROPS),21 1.5 episodes per 100 patient-years, both rates are much lower than the 9.8 episodes per 100 patient-years observed in the PROPS placebo group. Assuming that compliance in the PROPS approximated that of ours, why were the rates of pneumococcal bacteremia among the patients receiving prophylaxis in both studies so low?

Several answers are possible. First, clearly the population that benefits the most from prophylaxis, those younger than 5 years of age, are receiving it the most frequently. Second, it could be that the rate of infection among the placebo group in the PROPS was unexpectedly high. This seems unlikely, as rates of pneumococcal bacteremia prior to the introduction of penicillin prophylaxis ranged from 5.8 to 11.6 episodes per 100 patient-years.20,21 Pneumococcal vaccination with the polysaccharide vaccine has probably done little to alter these rates, given the poor response to vaccination among patients with sickle cell disease demonstrated in the recent report by Bjornson et al.22 Third, it could be that prophylaxis decreases nasopharyngeal carriage of S pneumoniae. Recent data from Philadelphia, Pa,23 and Memphis, Tenn,24 however, demonstrate that 10% to 13% of their populations showed colonization, and in the series from Philadelphia,23 colonization did not differ between those receiving and not receiving prophylaxis. Finally, it could be that parents are starting prophylaxis when their children develop fevers, thus attenuating early pneumococcal bacteremia. Our data do not support this idea, as we found no difference in compliance between patients presenting to the emergency department with and without fevers.

In conclusion, we have demonstrated poor compliance with recommended penicillin prophylaxis against spontaneous pneumococcal bacteremia in a closely managed population of patients with sickle cell disease. Children older than 5 years and children covered by public insurance are at risk for particularly poor compliance. Our data suggest that efforts are necessary to improve compliance in all groups through vigorous medical and social service intervention. Such an effort merits further study.

Accepted for publication September 29, 1997.
Corresponding author: Stephen J. Teach, MD, MPH, Emergency Medical Trauma Center, Children’s National Medical Center, Suite 1450, 111 Michigan Ave NW, Washington, DC 20010 (e-mail: teach@cnmc.org).

REFERENCES

**Correction**

Misspelling of Surname and Word in Reprint Address. In the “Picture of the Month” published in the December issue of the ARCHIVES (1997;151:1263-1264) Dr Yasemen Ergolü’s surname was misspelled in the table of contents, byline, affiliation footnote, and reprint address. Also the word “Mithatpaşa” was misspelled in the reprint address. Both misspellings were caused by a deficiency in the electronic conversion program. The journal apologizes for the error.