The New England
Journal of Medicine

Volume 314 JUNE 19, 1986 Number 25

PROPHYLAXIS WITH ORAL PENICILLIN IN CHILDREN WITH SICKLE CELL ANEMIA

A Randomized Trial

MARILYN H. GASTON, M.D., JOEL I. VERTER, PH.D., GERALD WOODS, M.D., CHARLES PEGELOW, M.D., JOHN KELLEHER, M.D., GERALD PRESBURY, M.D., HAROLD ZARKOWSKY, M.D., ELLIOTT VICHINSKY, M.D., RATHI IYER, M.D., JEFFREY S. LOBEL, M.D., STEVEN DIAMOND, M.D., C. TATE HOLBROOK, M.D., FRANCES M. GILL, M.D., KIM RITCHEY, M.D., AND JOHN M. FALLETTA, M.D., FOR THE PROPHYLACTIC PENICILLIN STUDY GROUP

Abstract Children with sickle cell anemia have an increased susceptibility to bacterial infections, especially to those caused by *Streptococcus pneumoniae*. We therefore conducted a multicenter, randomized, double-blind, placebo-controlled clinical trial to test whether the regular, daily administration of oral penicillin would reduce the incidence of documented septicemia due to *S. pneumoniae* in children with sickle cell anemia who were under the age of three years at the time of entry. The children were randomly assigned to receive either 125 mg of penicillin V potassium (105 children) or placebo (110 children) twice daily. The trial was terminated 8 months early, after an average of 15 months of follow-up, when an 84 percent reduction in the incidence of infection was observed in the group treated with penicillin, as compared with the group given placebo (13 of 110 patients vs. 2 of 105; P = 0.0025), with no deaths from pneumococcal septicemia occurring in the penicillin group but three deaths from the infection occurring in the placebo group. On the basis of these results, we conclude that children should be screened in the neonatal period for sickle cell hemoglobinopathy and that those with sickle cell anemia should receive prophylactic therapy with oral penicillin by four months of age to decrease the morbidity and mortality associated with pneumococcal septicemia. (N Engl J Med 1986; 314:1593-9.)

FOR 20 years, children with sickle cell anemia have been known to have an increased susceptibility to severe bacterial infections, particularly those due to *Streptococcus pneumoniae*. Meningitis, pneumonia, and septicemia caused by this organism have been recognized as the major causes of death among children with the disorder, with those under three years of age at highest risk.[1-5] The incidence of pneumococcal septicemia among children with sickle cell anemia under the age of five years appears to have remained remarkably constant, at 7 to 8 per 100 person-years of observation.[6-8] This illness is often fulminant, progressing from the onset of fever to death in less than 12 hours; the case fatality rate may be as high as 35 percent.[7,9,10]

The recent widespread availability of pneumococcal vaccines and improved programs of care for chil-

Address reprint requests to Dr. Gaston at the Sickle Cell Disease Branch, Federal Bldg., Rm. 504, 7550 Wisconsin Ave., Bethesda, MD 20892.

Sponsored by the Sickle Cell Disease Branch, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), Bethesda.

The clinical centers in the Prophylactic Penicillin Study (PROPS) group and their principal investigators and project coordinators were Interfaith Medical Center, Brooklyn — Steven Diamond, M.D., and Margaret Allen, R.N.; Boston City Hospital — Lillian McMahon, M.D., and Jane Luff, R.N.; Yale University, New Haven, Conn. — Kim Ritchey, M.D., and Yolanda Rooks, P.N.P.; Children's Hospital, Philadelphia — Frances Gill, M.D., and Cynthia Allen, R.N.; Children's Hospital, Washington, D.C. — John Kelleher, M.D., and Iola Williams, P.N.P.; Duke University, Durham, N.C. — John Falletta, M.D., and Marilyn Hockenberry, R.N.; University of Miami — Charles Pegelow, M.D., and Mavis Eaton, P.N.P.; Michael Reese Hospital, Chicago — Nasrin Talishy, M.D., and Joyce Meyers, R.N.; Washington University, St. Louis — Harold Zarkowsky, M.D., and William Bishop, P.N.P.; University of Tennessee — St. Jude Children's Research Hospital, Memphis — Gerald Presbury, M.D., and Julie Dahl, R.N.; Children's Hospital, Oakland, Calif. — Elliott Vichinsky, M.D., and Ann Earles, P.N.P.; San Francisco General Hospital — William Lande, M.D., and Patricia Gibbons, P.N.P.; Children's Hospital, Cincinnati — Jeffrey Lobel, M.D., and Eula Hawkins, R.N.; University of South Alabama, Mobile — Vipul Mankad, M.D., and Patricia Davis, R.N.; University of Illinois, Chicago — Sudha Rao, M.D., and Sandra Gooden, R.N.; Children's Mercy Hospital, Kansas City, Mo. — Gerald Woods, M.D., and Wanda Boyd, R.N.; East Carolina University, Greenville, N.C. — C. Tate Holbrook, M.D., and Cindy Gaskins; University of Mississippi, Jackson — Rathi Iyer, M.D., and Jennie Nugent; Arkansas Children's Hospital, Little Rock — Dasilee H. Berry, M.D., and Kathryn Bailey, R.N.; University of Alabama, Birmingham — Robert Castleberry, M.D., and Nancy Brown, R.N.; Grady Memorial Hospital, Atlanta — Iris Buchanan, M.D., and JoAnn Harris, R.N.; Children's Memorial Hospital, Chicago — Helen Maurer, M.D., and Carol Ingrisano, R.N.; and the Sickle Cell Comprehensive Center, Milwaukee — Betty Malone, M.D., and Denise Lockhart, R.N. The chairman of the PROPS group was John Falletta, M.D., Duke University, the staff at the project office (NHLBI) were Marilyn H. Gaston, M.D., and Sharon Brown, B.S., and the staff at the Data Coordinating Center (NHLBI) were Joel Verter, Ph.D., and Pat Strobell. The Policy Advisory Board consisted of Harold Ballard, M.D. (chairman), Darleen Powars, M.D., Marcus Kjelsberg, Ph.D., George Honig, M.D., Helen Ranney, M.D., Andrew Keller, M.D., Wendell Rosse, M.D., Paul Levy, Ph.D., and Clarice Reid, M.D. Participants at the National Hemoglobinopathy Laboratory (Centers for Disease Control) were Rosalie Baine, Ph.D., and Solomon Holland, M.T. (A.S.C.P.); at the National Institute of Allergy and Infectious Diseases (NIH), Michael Frank, M.D., and Stephanie Simmons, M.T.; and at the Drug Dispensing Center (Duke University), Donald Holloway, Pharm.D.

dren with sickle cell anemia have led to the hope that the high risk of life-threatening pneumococcal infection in these patients can be markedly reduced. Indeed, some investigators have noted that an impressive decrease in mortality from pneumococcal septicemia has resulted from diagnosis of sickle cell anemia in the newborn period, closer medical supervision, and the prompt use of antibiotics in febrile children.[10-12] However, this experience is somewhat different from that observed during 1980 to 1981 by the Cooperative Study of Sickle Cell Disease, a nationwide multicenter study that has been described elsewhere.[13] In that investigation, among 335 children with sickle cell anemia under three years of age in 21 institutions in the United States, the annual incidence of pneumococcal septicemia was 10 per 100 person-years, with a 30 percent case fatality rate, thereby reflecting virtually no change in the severity of pneumococcal infection among children with sickle cell anemia in the past 20 years.

Prophylactic therapy with penicillin has been advocated as a preventive measure against severe pneumococcal infection in children with sickle cell anemia. In 1983, members of the Cooperative Study of Sickle Cell Disease initiated a study of the effectiveness of prophylaxis with oral penicillin in such children; this report is based on that study.

Methods

Organization

The Sickle Cell Disease Branch, Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute, established the Prophylactic Penicillin Study (PROPS) group in 1983 to assess the efficacy of oral penicillin in preventing severe bacterial infection in children with sickle cell anemia. The study group included 12 clinical centers that had participated in the Cooperative Study of Sickle Cell Disease and 11 other clinical institutions. The National Hemoglobinopathy Laboratory, Centers for Disease Control, provided the diagnostic evaluation of hemoglobin by performing cellulose acetate electrophoresis and citrate agar electrophoresis on hemoglobin from each patient on entry into the trial. If appropriate, quantitative chromatography for hemoglobin A_2 was also performed. The Laboratory of Clinical Investigations, National Institute of Allergy and Infectious Diseases, National Institutes of Health measured antibody titers to *S. pneumoniae* and urine penicillin levels, and serotyped isolated organisms. The penicillin was donated by Wyeth Laboratories and distributed by the Duke University Hospital Pharmacy to each center.

The trial was monitored by the program office of the Sickle Cell Disease Branch, and the PROPS Data Coordinating Center, Biometrics Research Branch, Division of Epidemiology and Clinical Applications, National Heart, Lung, and Blood Institute. The existing policy board of the Cooperative Study of Sickle Cell Disease, whose members have expertise in hematology, epidemiology, and biostatistics, was chosen to act as an independent advisory board to the Institute. During the study, the board's main tasks were to review and advise the Institute on the quality of the protocol, to review the entry into the study and the follow-up of patients, to review end-point and side-effect data at least twice a year, to review the performance of the clinical centers, and to make recommendations for early termination of the study.

Design

The PROPS was a multicenter, randomized, double-blind, placebo-controlled clinical trial designed to test whether the administration of oral penicillin twice a day would reduce the incidence of documented bacterial infection in a population of children with sickle cell anemia who were under three years of age at admission into the study.

Children 3 to 36 months old with an SS hemoglobin pattern on electrophoresis and varying amounts of fetal hemoglobin were eligible for random assignment into either the penicillin or the placebo group. All hemoglobin phenotypes were confirmed at the Centers for Disease Control. Patients entered the trial at a time when they were free from any signs or symptoms of infection; they were excluded if they were receiving long-term antibiotic or transfusion therapy or if they had a known allergy to penicillin. The children in the group that received penicillin were given 125-mg tablets of penicillin V potassium twice a day, beginning immediately on entry into the trial. The children in the placebo group were given 50-mg tablets of vitamin C, which were nearly identical in appearance to the penicillin tablets and which were to be administered according to the same schedule that was used for the active drug. All tablets were crushed and administered with food.

The PROPS Data Coordinating Center generated the randomization numbers for each clinical site, and with the help of the program office, directed patient-entry assignments by means of telephone contact. Sealed envelopes that were stored at the clinical centers were available as a back-up for randomization when telephone contact was not possible, but they were rarely used. The randomization schedules were prepared with use of the method of blocked randomization[14] within each clinic to ensure balance in numbers between the two groups. Parents were informed of the objectives of the investigation, and their informed consent had to be obtained before a child could be assigned to a group. Neither the parents nor the center personnel were informed of the content of the tablets.

The same protocol was used by all the clinical centers. The patients were seen on entry into the trial and at subsequent visits that were arranged according to their routine schedule of care — i.e., every three months. At every patient visit, a history was taken and a physical examination was performed, as were a complete blood count, a pill count to assess adherence to the drug regimen, and a urine collection for determination of penicillin levels. The urine determination was performed by the reference laboratory, which used the *Micrococcus lutea* inhibition technique[15]; this assay detects penicillin up to 18 to 24 hours after administration. In addition, the occurrence of any febrile events was ascertained, and trial medication was dispensed. On entry into the study and on exit from the study, nasopharyngeal samples for culture and serum samples for pneumococcal antibody assessments were obtained. The data were noted on standard forms and sent to the PROPS Data Coordinating Center. Urine was collected on filter paper by the patient's family midway between scheduled clinic visits, or every six weeks, for determinations of the presence of penicillin. At each visit, the patient's parent or guardian was reminded of the importance of giving the medication according to the protocol, and telephone calls were made to the families between visits to encourage compliance.

Each time a child was evaluated for a severe bacterial infection, the protocol required that samples of blood and other appropriate tissues be obtained for culture and that urine be collected for determination of the presence of the antibiotic. When *S. pneumoniae* was isolated, the organism was identified by serotype, and a sample of serum was obtained from the patient for evaluation of pneumococcal antibody titers. If a child had a febrile illness (temperature >38.5°C) for which an antibiotic was prescribed, the trial medication was discontinued until the prescribed antibiotic course was completed; the study medication was then resumed. There was no standard protocol for the treatment of infections with antibiotics; this was left to the discretion of the principal investigator at each center.

The investigation was not designed to evaluate the effectiveness of the pneumococcal vaccine. However, it was clear at the beginning of the study that investigators were administering pneumococcal vaccine to subjects of various ages (range, 6 to 24 months). To standardize this regimen across all centers, the investigators agreed to administer the 14-valent pneumococcal vaccine (Pneumovax) uniformly, when the patient was one year of age and again at two years.

The 23-valent pneumococcal vaccine was substituted for the 14-valent vaccine when it became available at individual centers.

End Points

The primary end point of the study was a documented severe infection due to *S. pneumoniae*. The secondary end point was a documented severe infection due to an organism other than *S. pneumoniae*. Severe infections were defined as bacteremia, meningitis, and pneumonia requiring hospitalization. A documented bacterial infection was defined as an infection in which the clinical and laboratory findings were consistent with the diagnosis and an organism was cultured from an involved body fluid.

Statistical Analysis and Sample Size

A review of the literature failed to yield current estimates of the incidence of documented severe infection in children younger than three years. Therefore, a review of the infections reported in the Cooperative Study of Sickle Cell Disease was conducted. On the basis of an observed one-year incidence of 10 percent of documented pneumococcal septicemia, it was estimated that the same incidence could be expected in the placebo group. Additional assumptions included in the sample-size estimate were an 80 percent reduction in the infection rate, a one-sided Type I (α) error rate of 0.05, and a power of 0.80 (Type II error of 0.20). The assumptions resulted in a sample-size requirement of 108 patients in each study group (treatment and placebo), who had to be followed for a minimum of one year. Comparisons of base-line factors between groups were done with chi-square tests or t-tests, as appropriate. The Fisher exact test[16] was used to compare the proportions of documented severe infection in the two study groups. This comparison was evaluated with use of a one-tailed test of significance, which was appropriate for the design assumptions that were made. The Mantel–Haenszel test[17] allowed comparison of the proportions of infections between the groups, after adjustment for potential risk factors (e.g., age). Cox regression models[18] were used to assess differences in time to episode of infection between the penicillin and placebo groups.

Monitoring

The policy and data monitoring board of the Comparative Study of Sickle Cell Disease met five times before the termination of the study. By the third meeting, only six end points had occurred, and no formal review of the data took place. A thorough review of the cumulative end-point results and a consideration of early termination took place at the fourth meeting. To aid in the board's deliberations, an analysis based on the method of Halperin et al. was presented.[19] This method, although it does not actually yield an adjusted P value, addresses the problem of multiple examinations of the data. The method allowed the board to consider the conditional probability that the PROPS would yield a statistically significant result in February 1986, given the results available at the monitoring times and the projected distribution of end points in the future. Thus, if the treatment effect observed for the remainder of the study was assumed to be less than the current estimate but the conditional power was high (e.g., >85 percent), then the board could feel confident that the current statistically significant difference would not be altered by early termination of the study.

Results

Patient recruitment began in August 1983, and randomization and entry of 219 children into the trial were completed on February 28, 1985. Clinical centers recruited the children from among their own patients with sickle cell anemia, from referrals from outside physicians, and from among newborns with an SS hemoglobin pattern identified by neonatal screening programs. Subsequently, revisions of the genotype led to the withdrawal of four children admitted to the trial (three who had been assigned to the placebo group and one who had been assigned to the penicillin group). These children did not have any documented severe infections and are not included in this analysis. Thus, this report includes observations in 215 patients (105 in the penicillin group and 110 in the placebo group). Three centers entered only 1 patient, and one center entered 26 patients; the average number of patients per center was 9.3. At the end of the trial, the status of all but one child was verified; the parents of that child, who was in the penicillin group, could not be contacted.

Table 1 describes the PROPS patient cohort at entry. Seventy-three percent were less than two years old (average age, 18 months). None of the variables measured at base line showed statistically significant differences between the placebo and penicillin groups. Approximately 70 percent of the children had received the pneumococcal vaccine at entry or before entry. Among the children who were older than one year, 93.2 percent in the placebo group and 95.2 percent in the penicillin group had received the vaccine.

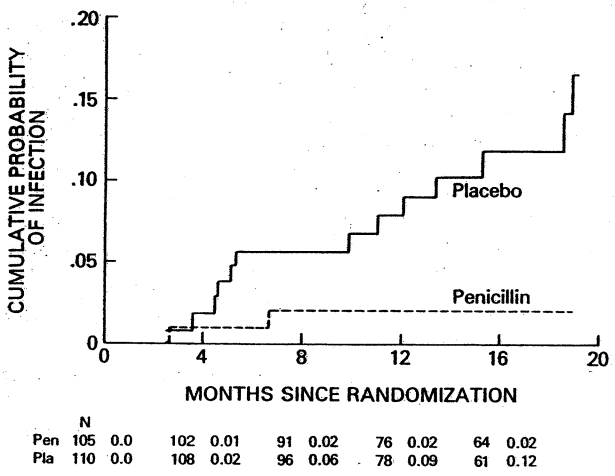
The trial was scheduled to end in February 1986, but it was terminated 8 months earlier (with an average of 15 months of follow-up), after the occurrence of 15 episodes of pneumococcal septicemia — 13 in the placebo group and 2 in the penicillin group. These episodes occurred in nine centers; there was no geographic clustering. There were no other documented severe bacterial infections due to *S. pneumoniae*. The observed 84 percent reduction in the incidence of infection in the group treated with penicillin yielded a nominal one-sided P value of 0.0025. Adjustments for potential risk factors that were done with use of time-

Table 1. Characteristics at Entry, According to Treatment Group.

Characteristic	Treatment Group	
	Penicillin (N = 105)	Placebo (N = 110)
	% of patients	
Age (mo)*		
3–5	15.4	10.8
6–11	23.1	21.6
12–17	14.4	20.7
18–23	22.1	17.1
≥24†	25.0	28.8
Boys	48.5	51.4
Palpable spleen	30.8	30.9
Pneumococcal vaccine	67.0	71.6
Previous infection		
Pneumonia	19.2	12.6
Bacteremia	5.8	5.4
Osteomyelitis	2.9	0
Meningitis	—	0.9
	mean values	
Laboratory findings		
Hematocrit (%)	26.1	27.3
Hemoglobin (g/dl)	8.8	9.1
White-cell count ($\times 10^{-9}$/liter)	14.6	14.1
Granulocytes (%)	31.7	35.0

*The mean value for age in the penicillin group was 17.8 months; that in the placebo group was 18.5.

†One child was older than 36 months.



	N									
Pen	105	0.0	102	0.01	91	0.02	76	0.02	64	0.02
Pla	110	0.0	108	0.02	96	0.06	78	0.09	61	0.12

Figure 1. Cumulative Infection Rates for All Patients in the Prophylactic Penicillin Study.

Numbers of patients at risk and infection rates in the penicillin (Pen) and placebo (Pla) groups, at four-month intervals, appear below the curves (one-tailed P value = 0.003).

to-event analysis yielded similar results. The observed one-year incidence of pneumococcal septicemia in the placebo group was 0.09. The penicillin group had an incidence of 0.02 (Fig. 1).

Eight of the 15 events occurred in children who were under the age of two years, five occurred in children who were two years old, and only two occurred in children who were three. In the placebo group, the observed rate per 100 person-years of observation decreased with increasing age (Table 2), with children under the age of three having 3.2 times the risk of those who had passed their third birthday. Reduction in the incidence of septicemia was seen in the children who received penicillin, regardless of whether they had received the vaccine. The reductions were observed in both the boys (83 percent) and the girls (84 percent).

Compliance in the PROPS was assessed by pill counts and urine tests. Approximately 66 percent of the scheduled appointments were kept by the subjects in both groups. The data on pill counts are not presented because of the difficulty in interpreting compliance when 34 percent of scheduled visits are not kept. The data on penicillin in the urine were also incomplete; only 31 percent of the expected number of urine samples were obtained. These samples were collected during both routine interim visits and febrile episodes. Unfortunately, the time of collection was often imprecisely noted, making accurate interpretation of overall compliance impossible.

The penicillin was well tolerated, and no confirmed allergic reactions to the antibiotic occurred.

Table 3 provides details about the 15 patients with severe pneumococcal infection. Each of the isolates of *S. pneumoniae* was sensitive to penicillin, although one isolate from a patient in the placebo group showed only moderate sensitivity (minimal inhibitory concentration, 0.25 μg per milliliter). Nine of the episodes of septicemia were associated with other known infections — five with pneumonia, two with meningitis, and two with otitis media.

The four children in the placebo group had a fulminant course; they proceeded from the onset of fever to death (three children) or septic shock (one child) in less than nine hours. Three of these patients had documented disseminated intravascular coagulation (one had visible diplococci on the peripheral-blood film), and one had postmortem findings indicative of Waterhouse–Friderichsen syndrome. The child who survived the disseminated intravascular coagulation had a cerebrovascular accident (a CT scan showed multiple cerebral infarctions with a major area of hemorrhage) and remains alive but with severe neurologic impairments. All three deaths in the placebo group were due to pneumococcal septicemia, and all three patients had received pneumococcal vaccine — one at 21 months of age and the others at less than one year of age (Table 3).

Eleven of the 12 children with documented pneumococcal septicemia who were older than one year had received the pneumococcal vaccine; 9 of them had received it before the age of two years. Of the 12 isolates available for serotyping from the vaccinated children, 9 had serotypes that were present in the vaccine but that are known to be poorly antigenic.[20-23]

Since episodes of nonpneumococcal bacterial septicemias were not the primary end points, they were not considered in the analysis, but information about those that occurred was recorded. Our patients did not receive the *Hemophilus influenzae* vaccine until late in this study, by which time documented septicemia due to *H. influenzae* type B had developed in three children (ages, 24 to 33 months). One was receiving penicillin, and two were in the placebo group. One of the children in the placebo group died after a fulminant course; disseminated intravascular coagulation and a cerebrovascular accident were documented. One *H. influenzae* isolate was observed to be resistant to ampicillin. In one 24-month-old child in the placebo group, documented pneumococcal septicemia also developed, four months after the *H. influenzae* septicemia. Thus, by the end of the trial, a total of 18 documented episodes of septicemia had occurred in 17 children.

Three episodes of septicemia occurred shortly after

Table 2. Rate of *Streptococcus pneumoniae* Septicemia per 100 Person-Years, According to Treatment Group.

AGE (YR)	RATE OF INFECTION*	
	PENICILLIN GROUP	PLACEBO GROUP
<1	0.0 (12.2)	20.1 (14.9)
1	2.2 (45.9)	9.1 (43.8)
2	0.0 (48.2)	10.8 (46.5)
3†	3.4 (29.8)	3.6 (27.6)
Total	1.5 (136.1)	9.8 (132.8)

*The figures in parentheses refer to the number of person-years at risk.

†Ninety percent of the person-years at risk in this group occurred in three-year-old children.

the trial was terminated. Documented pneumococcal septicemia occurred in a child older than three years of age who had been in the placebo group (Patient 16, Table 3). Another patient in the placebo group had meningitis and septicemia due to *Escherichia coli*, and one child in the penicillin group had *H. influenzae* septicemia with disseminated intravascular coagulation; this patient died.

Discussion

This randomized, double-blind, multicenter trial demonstrated the effectiveness of prophylaxis with oral penicillin in significantly decreasing the incidence of pneumococcal septicemia in children with sickle cell anemia (SS). The risk of septicemia from *S. pneumoniae* was decreased by 84 percent (13 of 110 patients vs. 2 of 105), and no deaths occurred in the group that received penicillin.

Although it has been suggested that prophylactic therapy with penicillin may provide protection against pneumococcal septicemia in children with splenic dysfunction[24-26] (and Brown AK: personal communication), no controlled studies have shown a benefit of the treatment until the recent trial by John et al.,[27] which suggested that the risk of pneumococcal septicemia in young children with splenic dysfunction could be reduced by the use of penicillin. Since most investigators have been concerned that compliance with a regimen of oral penicillin might be too unpredictable to permit detection of a benefit from oral penicillin, some studies, including the randomized trial by John et al., have employed intramuscular penicillin. In that trial, monthly administration of penicillin G benzathine (600,000 U) reduced pneumococcal septicemia in Jamaican children with sickle cell anemia who were younger than three years, although the difference between the infection rates in the treated and untreated groups was not statistically significant. Parenteral therapy ensures a known compliance rate, which could approach 100 percent if every monthly appointment was kept by the patient or if home visits were conducted by health care personnel. However, such compliance is unlikely in the present system of health care in most areas of the United States, and sustained compliance with monthly intramuscular injections is difficult because of the progressive reluctance of families to continue to allow their children to undergo the painful prophylactic injections. Indeed, John et al., terminated the treatment with penicillin in their study when each child reached 36 months of age, because of the problem of painful injections. In addition, this approach to prophylaxis may not provide adequate penicillin activity in the serum of some children at 18 to 30 days after the injection.[28] Therefore, the de-

Table 3. Characteristics of Patients with Documented Pneumococcal Septicemia.

Patient No.	Newborn Diagnosis of Sickle Cell Anemia	Age at Entry	Age at Infection	Pneumococcal Serotype	Age at Vaccination (Valence)	Associated Diagnosis	Outcome	Treatment Group
		mo	*mo*		*mo*			
1	+	10	12	23	—	Meningitis	Alive	Penicillin
2	+	31	38	—	15 (14)		Alive	Penicillin
3	+	4	6	—	—	Meningitis	Alive	Placebo
4	+	4	9	14	—	—	Alive	Placebo
5	+	7	11	19A	7 (23)	Disseminated intravascular coagulation*	Died	Placebo
6	+	9	13	6	11 (23)	Pneumonia,* Waterhouse–Friderichsen syndrome	Died	Placebo
7	+	4	19	14	—	Otitis media	Alive	Placebo
8	−	16	21	6	16 (23)	Pneumonia	Alive	Placebo
9	+	18	24	14	18 (14)	Otitis media	Alive	Placebo
10	−	15	25	23	15 (14)	Disseminated intravascular coagulation,* cerebrovascular accident	Alive	Placebo
11	+	8	27	16	17 (23)	Pneumonia	Alive	Placebo
12	+	10	28	—	12 (14); 24 (23)	Pneumonia	Alive	Placebo
13	−	20	32	6	18 (14)	Pneumonia	Alive	Placebo
14	+	22	33	15	21 (14)	Disseminated intravascular coagulation,* tricuspid atresia	Died	Placebo
15	+	27	40	15	24 (14)		Alive	Placebo
16†	+	17	38	—	12 (14); 24 (23)		Alive	Placebo

*Fulminant course.

†Occurred after termination of study.

sirability of a painless, continuous, readily available form of penicillin prophylaxis is apparent.

Even though oral prophylaxis may be more acceptable and may provide continuous antibiotic protection, ensuring patient compliance with a prescribed medication regimen is nearly impossible[10,24] without an intensive, individualized educational program.[29] We attempted to assess compliance through pill counts and periodic evaluation of urine samples for penicillin. Both approaches proved to be unsatisfactory. The medicine bottles were not consistently brought in for the pill counts, and less than one third the expected number of urine samples were collected. Because of this problem of inadequate and incomplete reporting, determination of the exact pattern of penicillin administration in our treatment group or of antibiotic usage in the children in the placebo group who became ill was not possible. However, we can assume that the children in the penicillin group received less of the antibiotic than was prescribed, as has been noted in most compliance studies of oral medicine use,[30-33] and that the subjects in the placebo group received antibiotics for most febrile illnesses, reflecting the common practice in the treatment of children with sickle cell anemia in this country. However, even with consideration of these factors, which would narrow the therapeutic differences between the two groups, we observed a dramatic reduction in the occurrence of pneumococcal septicemia among the patients who were treated with penicillin. It is possible that the availability of penicillin in the home, which allowed prompt administration at the first sign of a febrile illness, as well as irregular but continued use of the drug, are factors in our results.

Pneumococcal vaccine was administered in a standard fashion to patients in both groups. Although this study was not designed to test vaccine efficacy, the vaccine alone did not appear to provide protection against *S. pneumoniae* septicemia that was equivalent to the protection provided by the combination of penicillin and the vaccine. Such a finding is not surprising because the vaccine did not contain all the serotypes that cause infections in young children. Also, the children in the study who were younger than one year were not yet immunized, and the remaining children were likely to respond to fewer antigens and to have less of an immune response to any of the antigens than older children or adults.[24,25,34-37]

No complications from the oral penicillin prophylaxis were observed. Still to be determined are the potential long-term risks of prophylaxis; these may include delayed development of humoral immunity to the nonvaccine strains of pneumococcus, which would place children at higher risk of pneumococcal septicemia when they were older and prophylaxis was discontinued[23,27] (and Brown AK: personal communication). Another concern is the possible emergence of penicillin-resistant pneumococci as a result of long-term prophylaxis. However, we found no resistant pneumococci in the nasopharynx in our patients.

Eighty percent of the children in whom septicemia developed during the trial had been found to have sickle cell anemia in the neonatal period (Table 3). Despite this early diagnosis, the knowledge of the high risk of severe infection among these children, and the provision of comprehensive health care to the patients enrolled in this study, the sepsis-related case fatality rate in the placebo group was 23 percent (3 of 13 patients). Although other researchers have suggested the contrary,[8,11,12] these data and the observation of a 20 percent mortality rate from sepsis in the Cooperative Study of Sickle Cell Disease[38] clearly demonstrate that early diagnosis of sickle cell anemia, coupled with the provision of comprehensive health care, are by themselves insufficient to eliminate deaths from pneumococcal septicemia among young children with the disease. This can be partly attributed to the often overwhelming nature of the infection.[3,9,39,40] The onset can be subtle and can proceed rapidly to disseminated intravascular coagulation and shock, which is almost always fatal. The three children in our study who died (who were all in the placebo group) survived for only two to eight hours after they began to receive medical care. Thus, the most successful way to manage fulminant pneumococcemia in children with sickle cell anemia is to prevent it.

Our data strongly support the recommendation that neonatal detection of sickle cell anemia should be a high priority, since it is the first step in the prevention of morbidity and mortality due to severe bacterial infections among young children with SS hemoglobinopathy. Babies identified at birth as having an FS electrophoretic pattern should begin to receive prophylactic penicillin not later than four months after birth, since the youngest children in the Cooperative Study of Sickle Cell Disease who had pneumococcal septicemia were four to five months old.[38] Although data that identify the age at which prophylactic penicillin can safely be discontinued are not available, the experience to date indicates that prophylaxis should continue beyond the third birthday.[27]

We are indebted to Wyeth Laboratories, Philadelphia, for donating the penicillin, to Elizabeth Pitt for editorial assistance, and to Avis Hutchings, Janie McClellan, and Jean Makle for help in the preparation of the manuscript.

References

1. Robinson MG, Watson RJ. Pneumococcal meningitis in sickle-cell anemia. N Engl J Med 1966; 274:1006-8.
2. Eeckels R, Gatti F, Renoirte AM. Abnormal distribution of haemoglobin genotypes in negro children with severe bacterial infections. Nature 1967; 216:382.
3. Seeler RA, Metzger W, Mufson MA. Diplococcus pneumoniae infections in children with sickle cell anemia. Am J Dis Child 1972; 123:8-10.
4. Pearson HA. Sickle cell anemia and serious infections due to encapsulated bacteria. J Infect Dis 1977; 136:Suppl:S25-S30.
5. Barrett-Connor E. Bacterial infection and sickle cell anemia: an analysis of 250 infections in 166 patients and a review of the literature. Medicine (Baltimore) 1971; 50:97-112.
6. Powars DR. Natural history of sickle cell disease — the first ten years. Semin Hematol 1975; 12:267-85.
7. Overturf GD, Powars D, Baraff LJ. Bacterial meningitis and septicemia in sickle cell disease. Am J Dis Child 1977; 131:784-7.

7. Powars D, Overturf G, Weiss J, Lee S, Chan L. Pneumococcal septicemia in children with sickle cell anemia: changing trend of survival. JAMA 1981; 245:1839-42.
8. Kabins SA, Lerner C. Fulminant pneumococcemia and sickle cell anemia. JAMA 1970; 211:467-71.
9. Seeler RA. Deaths in children with sickle cell anemia: a clinical analysis of 19 fatal instances in Chicago. Clin Pediatr 1972; 11:634-7.
10. Lobel JS, Cameron BF, Johnson E, Smith D. The value of screening umbilical cord blood for hemoglobinopathy. Ohio State Med J 1984; 80:140-2.
11. Grover R, Shahidi S, Fisher B, Goldberg D, Wethers D. Current sickle cell screening program for newborns in New York City, 1979–1980. Am J Public Health 1983; 73:249-52.
12. Gaston M, Rosse WF. The cooperative study of sickle cell disease: review of study design and objectives. Am J Pediatr Hematol Oncol 1982; 4:197-201.
13. Friedman LM, Furberg CD, Demets DL. Fundamentals of clinical trials. Boston: John Wright/PSG, 1981:43-5.
14. Markowitz M, Gordis L. A mail-in technique for detecting penicillin in urine: application to the study of maintenance of prophylaxis in rheumatic fever patients. Pediatrics 1968; 41:151-3.
15. Fisher RA. Statistical methods for research workers. 11th ed. New York: Hafner, 1950:96-101.
16. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. JNCI 1959; 22:719-48.
17. Cox DR. Regression models and life tables. J R Stat Soc [B] 1972; 34:187-220.
18. Halperin M, Lan KK, Ware JH, Johnson NJ, DeMets DL. An aid to data monitoring in long-term clinical trials. Controlled Clin Trials 1982; 3:311-23.
19. Cowan MJ, Ammann AJ, Wara DW, et al. Pneumococcal polysaccharide immunization in infants and children. Pediatrics 1978; 62:721-7.
20. Overturf GD, Selzer JW, Chan L, et al. Pneumococcal polysaccharide immunization of children with sickle cell disease. II. Serologic response and pneumococcal disease following immunization. Am J Pediatr Hematol Oncol 1982; 4:25-35.
21. Ammann AJ, Addiego J, Wara DW, Lubin B, Smith WB, Mentzer WC. Polyvalent pneumococcal-polysaccharide immunization of patients with sickle-cell anemia and patients with splenectomy. N Engl J Med 1977; 297:897-900.
22. Weibel RE, Vella PP, McLean AA, Woodhour AF, Davidson WL, Hilleman MR. Studies in human subjects of polyvalent pneumococcal vaccines. Proc Soc Exp Biol Med 1977; 156:144-50.
23. Ahonkhai VI, Landesman SH, Fikrig SM, et al. Failure of pneumococcal vaccine in children with sickle-cell disease. N Engl J Med 1979; 301:26-7.
24. Buchanan GR, Schiffman G. Antibody responses to polyvalent pneumococcal vaccine in infants with sickle cell anemia. J Pediatr 1980; 96:264-6.
25. Landesman SH, Rao SP, Ahonkhai VI. Infections in children with sickle cell anemia. Special reference to pneumococcal and salmonella infections. Am J Pediatr Hematol Oncol 1982; 4:407-15.
26. John AB, Ramlal A, Jackson H, Maude GH, Waight Sharma A, Serjeant GR. Prevention of pneumococcal infection in children with homozygous sickle cell disease. Br Med J 1984; 288:1567-70.
27. Ginsburg CM, McCracken GH Jr, Zweighaft TC. Serum penicillin concentrations after intramuscular administration of benzathine penicillin G in children. Pediatrics 1982; 69:452-4.
28. Buchanan GR, Siegel JD, Smith SJ, DePasse BM. Oral penicillin prophylaxis in children with impaired splenic function: a study of compliance. Pediatrics 1982; 70:926-30.
29. Gordis L, Markowitz M, Lilienfeld AM. Studies in the epidemiology and preventability of rheumatic fever. IV. A quantitative determination of compliance in children on oral penicillin prophylaxis. Pediatrics 1969; 43:173-82.
30. Bergman AB, Werner RJ. Failure of children to receive penicillin by mouth. N Engl J Med 1963; 268:1334-8.
31. Gordis L, Markowitz M, Lilienfeld A. Why patients don't follow medical advice: a study of children on long-term antistreptococcal prophylaxis. J Pediatr 1969; 75:957-68.
32. Christensen DB. Drug-taking compliance: a review and synthesis. Health Serv Res 1978; 13:171-87.
33. Broome CV. Efficacy of pneumococcal polysaccharide vaccines. Rev Infect Dis 1981; 3:Suppl:S82-S96.
34. Overturf GD, Field R, Edmonds R. Death from Type 6 pneumococcal septicemia in a vaccinated child with sickle-cell disease. N Engl J Med 1979; 300:143.
35. Broome CV, Facklam RR, Fraser DW. Pneumococcal disease after pneumococcal vaccination: an alternative method to estimate the efficacy of pneumococcal vaccine. N Engl J Med 1980; 303:549-52.
36. Kaplan J, Frost H, Sarnaik S, Schiffman G. Type-specific antibodies in children with sickle cell anemia given polyvalent pneumococcal vaccine. J Pediatr 1982; 100:404-6.
37. Zarkowsky H, Gallagher D, Gill F, et al. Bacturemia and sickle hemoglobinopathies. J Pediatr (in press).
38. McDonald CR, Eichner ER. Concurrent primary pneumococcemia, disseminated intravascular coagulation, and sickle cell anemia. South Med J 1978; 71:858-60.
39. Gilman WL, Macdougall LG, Judisch JM. Sickle cell disease and disseminated intravascular coagulation: report of a childhood case. Clin Pediatr 1973; 12:600-2.