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Brief Review Article

Penicillin Prophylaxis in Children with Sickle Cell Disease

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Children who have sickle cell disease and are under the age of five years are at increased risk of life-threatening pneumococcal infection due to absent or non-functional spleens and a decreased immune response. To prevent pneumococcal infection, the American Academy of Pediatrics recommends the use of penicillin prophylaxis in children with sickle cell disease under the age of five and in older children who have had a previous severe pneumococcal infection or have functional/surgical asplenia. These recommendations are based on two landmark studies, the first evaluating the effectiveness of penicillin prophylaxis and the second evaluating the duration of prophylaxis. Although the mortality rate from infection has been reduced following penicillin prophylaxis, altered immunologic response and penicillin-resistant *S. pneumoniae* remain a concern. This paper will review the literature that supports the use of penicillin prophylaxis, potential problems associated with prolonged therapy and recommendations for prophylaxis.

KEYWORDS penicillin, prophylaxis, sickle cell disease

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BACKGROUND

According to the World Health Organization, hemoglobinopathies are the most common inherited disorder in the world.[1] The primary hemoglobin disorder, sickle cell disease (SCD), is a recessively inherited disorder found in African, Mediterranean, Middle Eastern, Indian, Asian, Caribbean, and South and Central American populations and their descents.[2,3] Approximately 300,000 children worldwide are born with this disorder each year.[4] In the United States, approximately 1 in 375 African American newborns have SCD and another 7%-8% of Americans of African and Caribbean descent carry the sickle cell trait.[5] After the benefits of early screening were discovered in the mid-1980s, testing for SCD became a component of routine newborn screening in the United States.[6]

Patients with both recessive genes for SCD are designated as hemoglobin SS and have the most severe form of the disease, sickle cell anemia (SCA). The sickle cell gene carries a single mutation leading to the substitution of valine for glutamic acid at the sixth amino acid position of the β globin chain of the hemoglobin tetramer (2-α globin and 2-β globin chains).[7] This mutated hemoglobin molecule is designated HbS. When the hemoglobin molecule is in the oxygenated state, HbS functions normally. However, in the deoxygenated state, the substituted valine on HbS binds to other adjacent β globin molecules, resulting in highly ordered molecular polymers. These polymers elongate into filamentous struc-

ABBREVIATIONS PCV, pneumococcal conjugate vaccine; PPSV, pneumococcal polysaccharide vaccine; PROPS, Prophylactic Penicillin Study Group; SCA, sickle cell anemia; SCD, sickle cell disease; TMP-SMX, trimethoprim-sulfamethoxazole

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tures which aggregate to form rigid, crystal-like rods. These rods form the characteristic sickle cell shape. These "sickled" red blood cells can revert back to their normal shape when reoxygenation occurs.[1] However, with repeated sickling, the red blood cell membrane eventually becomes permanently damaged and irreversible sickling occurs. These sickle cells become trapped in smaller blood vessels and prevent the flow of blood to various parts of the body.

One of the most detrimental effects of sickling is vaso-occlusion within the spleen, which results in functional asplenia in 94% of SCA patients by the age of five years.[8] With functional asplenia, the patient can no longer filter waste products such as damaged sickle cells or bacteria from the blood.[8] The spleen is especially important in the removal of encapsulated organisms in children under the age of two who are unable to develop antibodies to encapsulated organisms (e.g., *Streptococcus pneumoniae).*[9] *Streptococcus pneumoniae* infections often progress quickly with death in less than 24 hours from onset.[5] In addition to filtering damaged red blood cells and bacteria from the blood, the spleen produces opsonins (e.g., complement, antibodies, and C-reactive protein) that bind to bacteria to trigger phagocytosis.[8] Functional asplenia thus further impairs the immune response of children with SCD.

Younger children with SCD are often more susceptible to infection by encapsulated organisms such as *S. pneumoniae* (66%), *Haemophilus influenzae*, and *Salmonella* species, while older children with SCD are affected more often by gram-negative enteric organisms (50%) such as *Escherichia coli*.[1,6,10] Before the use of routine penicillin prophylaxis, the case fatality in the United States was as high as 35%,[11] with *S. pneumoniae* infections often progressing quickly to death in less than 24 hours from onset.[5] Historically, the risk of infection among children younger than 5 years of age with SCD has been 3.2 to 6.9 events per 100 patient-years.[12] Following the addition of penicillin prophylaxis for SCD patients younger than 5 years of age, the rate of infection for *S. pneumoniae* has decreased to 1.5 events per 100 patient-years.[11] The mortality rate is now 11%-24% and is associated with *S. pneumoniae* septicemia and meningitis.[12]

Penicillin prophylaxis and vaccines against various serotypes of *S. pneumoniae* have been used to prevent infection with *S. pneumoniae* in SCD patients.[6] Over the years, penicillin prophylaxis has proven to be more effective than vaccination.[1] This, however, may be changing with the increase in resistant *S. pneumoniae* and the wide-spread use of the 7-valent conjugated *S. pneumoniae* vaccine (Prevnar; Wyeth Pharmaceuticals, Madison, NJ) which produces effective immunologic response in children under the age of two years.[13]

PREVENTION OF INFECTION

The first study to report the effectiveness of penicillin prophylaxis formed the foundation of the guidelines for penicillin prophylaxis in SCD.[11] This study was conducted by the Prophylactic Penicillin Study (PROPS) Group, which was established by the Sickle Cell Disease Branch, Division of Blood Diseases, and Resources of the National Heart, Lung, and Blood Institute. The purpose of the study was to assess the efficacy of penicillin prophylaxis in the prevention of severe bacterial infections in children with SCA.

The study was a multi-center, randomized, double-blinded, placebo-controlled clinical trial conducted in the United States between August 1983 and June 1985. Children were included in the study if they were between 3 and 36 months of age at randomization. Those in the penicillin group (n=105) received penicillin V potassium 125 mg twice daily, while patients in the placebo group (n=110) received vitamin C 50 mg twice daily. To help in administration of the study medication, all tablets were crushed and added to food.

Every three months, patients returned for a full history and physical examination including a complete blood count. A pill count was performed to assess compliance to therapy and a urine sample was obtained to determine penicillin concentration. Upon entry and completion of the study, nasopharyngeal cultures and immunological serum samples for antibody response were obtained. If a patient became ill during the study, cultures were taken to identify the organism and determine its sensitivity to antibiotic therapy. Urine samples were also collected to assess compliance with penicillin therapy. The primary end point of the study was a reduction in the incidence of severe *S. pneumoniae* infections. A secondary end point was a decrease in the number of severe infection caused by any other organism.

The study was terminated 8-months early due to an 84% reduction in *S. pneumoniae* infection and the absence of any fatalities in the group taking penicillin prophylaxis (p=0.0025). During the trial, 15 patients developed pneumococcal septicemia, 2 in the penicillin group and 13 in the placebo group. These infections occurred primarily in the younger children with 53.3% occurring in those younger than 2 years of age, 33.3% in those who were 2 to 3 years of age, and 13.3% who were greater than 3 years old. All isolates were sensitive to penicillin.

Four of the infected children who received placebo developed fulminant disease. Three of these patients proceeded from onset of fever to death in less than 9 hours. The fourth patient progressed from onset of fever to septic shock in the same amount of time. This child survived but had severe neurological impairment due to a cerebrovascular accident. No deaths occurred in the penicillin treated group. An important limitation to this study was the difficulty in determining compliance with penicillin prophylaxis therapy. Compliance was hard to determine since urine samples were collected for only 31% of scheduled return appointments, and pill counts were inaccurate because patients missed 34% of their scheduled return appointments. No allergic reactions were reported, and penicillin prophylaxis was well tolerated.

The authors concluded penicillin prophylaxis would drastically reduce the risk of pneumococcal infection in children with SCA, especially those under the age of three. They also noted the earlier penicillin prophylaxis begins, the more likely it is to be effective since the risk of infection is inversely related to age. In addition, even though compliance of penicillin therapy could not be accurately assessed, Gaston and colleagues suggested that infection rates decreased since parents could administer penicillin at the first signs of febrile illness in the patient with SCA. Another outcome of the PROPS trial was the advocacy for sickle cell testing as a standard component of newborn screenings.[14] This early diagnosis of SCD allowed practitioners to initiate penicillin prophylaxis before the age of 4 months.[14]

DOSES FOR PENICILLIN PROPHYLAXIS

In the PROPS study, all patients received penicillin V potassium 125 mg twice daily. This has become the dose recommended for children younger than 5 years of age.[15,16] In patients over the age of 5 years, penicillin V potassium 250 mg twice daily is suggested.[16] Children should be started on penicillin prophylaxis once the diagnosed is established or at least by 2 months of age.[16] Penicillin suspension can be used in place of penicillin tablets, but the shelf-life of the reconstituted suspension is only 14 days.[17] If compliance is considered to be a problem, monthly injections of 600,000 units of benzathine penicillin IM have been used in Jamaica.[18] However, these injections are painful, and the effectiveness of the injection for the later half of the month is questionable.[11] Amoxicillin 20 mg/kg/day is an alternative to penicillin.[16] For patients who are allergic to penicillin, erythromycin 125 mg twice daily is given to children younger than 5 years of age, and erythromycin 250 mg twice daily is given to children 5 years of age or older.[18]

DURATION OF PENICILLIN PROPHYLAXIS

Older children experience a dramatic decline in the incidence of pneumococcal infection when compared to children less than 5 years of age. This is thought to be a result of older children's increased ability to produce an immunologic response to encapsulated organisms such as *S. pneumoniae*.[11,19] In addition, there are concerns about higher rates of penicillin-resistant organisms associated with the use of penicillin prophylaxis in older children who no longer have the same risk of pneumococcal infection.

To determine whether penicillin prophylaxis should be continued for children with SCA after the 5 years of age, the Prophylactic Penicillin Study Group conducted PROPS II.[19] This was a randomized, double-blinded, placebo-controlled trial to evaluate the effects of discontinuation of penicillin prophylaxis at 5 years of age in children who had received penicillin prophylaxis for at least two years prior to enrollment into the study. Patients were seen or contacted every three months in order to obtain medical history and dispense study medication. If a child experienced a febrile illness, they were examined and blood was collected for cultures. Those who continued penicillin prophylaxis (n=201) received penicillin V potassium 250 mg twice daily. Those randomized to have their penicillin prophylaxis discon-

tinued (around the time of their fifth birthday; n=199) received a matching placebo that was administered twice daily.

Of the 400 patients enrolled in the study, 6 children experienced systemic infections caused by *S. pneumoniae*. Four of the six patients who developed an infection were in the placebo group (2% of the placebo group) while 2 were in the penicillin prophylaxis group (1% of the penicillin prophylaxis group). This resulted in a relative risk of infection of 0.5 (95% CI, 0.1–2.7). None of the 6 patients died from the infection. One patient in each group had a resistant strain of bacteria. Infections caused by other organisms occurred in 5 additional children (e.g., *H. influenzae* type b, *Salmonella* species, and group A β-hemolytic streptococci).

The observed rate of pneumococcal infection in this trial was less than the observed rate in the original PROPS study (0.33 per 100 patient-years vs. 1.5 per 100 patient-years, respectively). This difference was attributed to the younger age of participants in the PROPS study (3 to 36 months of age at randomization). This study lent support to the notion that penicillin prophylaxis should be discontinued in older children. Researchers of the PROPS II trial concluded children with SCA who are over the age of 5 years may have their penicillin prophylaxis discontinued, provided that they have not previously had a severe pneumococcal infection or functional asplenia. The American Academy of Pediatrics is in agreement with these conclusions.[16] Continued health maintenance visits are still required and diligent monitoring for the first signs and symptoms of a febrile infection are warranted.

CONCERNS REGARDING PENICILLIN PROPHYLAXIS IN SCD

Compliance/Education

As shown in the PROPS study, compliance with penicillin prophylaxis is often quite difficult to maintain.[11] Obviously, children have an increased risk of infection during periods when they do not take penicillin. Buchanan and Smith noted the importance of twice daily penicillin administration.[20] Over a 7-year period, they followed 88 children with SCA who received penicillin prophylaxis and observed eight episodes of pneumococcal septicemia in 6 of the 88 patients. In all but one case, the children were not taking penicillin at the time of infection. In this single patient, only a few doses of penicillin were missed prior to the onset of symptoms. According to the parents, only 6 to 48 hours had passed since the last dose of penicillin was given. Additional studies have reported that rapid colonization and infection can occur after one missed dose (approximately 10 to 20 hours without penicillin therapy).[21] The average compliance rate for penicillin prophylaxis is 66%–69%.[22] The highest medication compliance rates have been reported for children less than 5 years of age when the risk of dangerous infections is at its greatest.[17,22,23] Through education such as informative presentations to parents/caregivers regarding the pathogenesis of sickle cell disease, its complications, and the importance of penicillin prophylaxis, compliance rates as high as 82% have been achieved.[22]

The importance of education materials designed specifically for parents/caregivers of SCD children and children with SCD was studied by Mahat and colleagues.[24] An educational manual titled *Sickle Cell Disease: A Family Guide* (SCDFG) was written by members of the Sickle Cell Advisory Committee of the New Jersey Department of Health and Senior Services, Special Child Health and Early Intervention Services. The first edition of the manual provided general information on SCD, defined medical terms related to SCD, and listed treatment centers. With a grant from the New Jersey Department of Health and Senior Services, a second edition of the manual was developed by the Valerie Fund Children's Center. This second edition was based on the needs of the target population of parents/caregivers of SCD children and children with SCD and aimed to achieve behavioral changes beneficial to SCD patients. The expanded content of the revised edition included information of the diagnosis of SCD, complications, prevention, special treatment for problems related to SCD, and resources for assistance in an easy to read format with illustrations. Mahat and colleagues reported on a survey conducted on 48 parents/caregivers to evaluate the effectiveness of the revised manual. Seventy-five percent of parents/caregivers reported they thought the manual with easy to understand; 94% reported all the needed information about SCD could be found in the manual; 96% followed the instruction in the manual; 42% reported they found the information in the manual to be very helpful while 54%

reported they found the information to be a little helpful, and 58% reported they felt confident in the management of their children SCD. Further, the parents/caregivers increased knowledge correlated to a perceived improvement in care of the SCD patients: only 66% of children missed one to three days of school per academic year and only a few of children (number not specified) were admitted to the hospital more than three times in the previous year.

Altered immunological response

Some fear penicillin prophylaxis may reduce the immunologic response to the pneumococcal vaccine. Bjornson and colleagues studied the effects of penicillin prophylaxis on the immunoglobulin G (IgG) response of patients with SCD who were given the pneumococcal vaccine.[25] They found that the immunologic response to the 23-valent pneumococcal vaccine was poor despite a booster dose of the vaccine. However, administration of penicillin prophylaxis did not affect the IgG response. This concern for reduction of immunologic response has not been studied for the newer pneumococcal conjugate vaccine.

Penicillin-resistant S. pneumoniae

Another concern regarding penicillin prophylaxis is the emergence of penicillin-resistant *S. pneumoniae* and the colonization of the nasopharynx with these resistant strains. In North America, the incidence of resistant *S. pneumoniae* increased from 5% in 1989 to 35% in 1997.[8] Of the isolates in 1997, 25% were classified as intermediately resistant (MIC = 0.1–1 μg/mL) and 11% were classified as highly resistant (MIC ≥ 2 μg/mL). There is clear evidence that the use of penicillin prophylaxis in children with SCD decreases the colonization of the nasopharynx with *S. pneumoniae*. Anglin and colleagues discovered children with SCA had pneumococcal carriage rates of 8.7% versus 40.5% in age-matched African-American children without SCA (p=0.005).[21] This study did not show emergence of resistant pneumococcal colonization in children with SCA who received penicillin prophylaxis; however, more recent studies have reported the emergence of resistant pneumococcal colonization in the sickle cell population.

Steele and colleagues reported that 12% of children with SCD who received penicillin prophylaxis (42 carriers in 351 SCD patients) were colonized with *S. pneumoniae* in the nasopharynx, and 62% of these strains were classified as penicillin resistant (33% intermediate resistant, 29% highly resistant).[26] The investigators compared these colonization rates to children without SCD and found that 35% of children without SCD (86 carriers in 245 control patients) were colonized with *S. pneumoniae* in the nasopharynx and that 41% of these strains were classified as penicillin resistant (p=0.01). Thirty percent of penicillin-resistant isolates found in both groups were also resistant to other antibiotics such as the cephalosporins and trimethoprim-sulfamethoxazole (TMP-SMX). Overall colonization with resistant bacterial strains was not different between the two groups (7% for SCD patients vs. 12% for patients without SCD, p=0.05). Similarly, Norris and colleagues reported 10% colonization rate in those with SCD who received penicillin prophylaxis. However, only 33% of isolates (11/33) were classified as penicillin resistant with 12% of isolates (4/13) also resistant to cefotaxime.[27] Practitioners have become increasingly aware of the number of *S. pneumoniae* strains resistant to penicillin and other antibiotics (e.g., cephalosporins, TMP-SMX) and have begun to use vancomycin as empiric therapy in SCD patients who are hospitalized for an acute febrile illness.[28]

Impact of Pneumococcal Conjugate Vaccine

Prior to 2000, children with SCD greater than 2 years of age received the pneumococcal polysaccharide vaccine (PPSV) at 2 years of age, at 5 years of age, and again every 10 years.[29] This provided additional immunity against potential deadly pneumococcal disease in this at-risk population. However, in February 2000, a new 7-valent pneumococcal conjugate vaccine (PCV) was introduced.[30] It was recommended for all children less than 2 years of age and for selected high-risk children between 2 and 4 years of age, such as children with SCD. The PCV provided further coverage against potential deadly pneumococcal disease in an even younger group of SCD patients. Since this vaccine was also introduced into the regular pediatric vaccine schedule recommended by the Centers for Disease Control Prevention for all children, it has had a significant impact on pneumococcal disease in the United States and other countries were the vaccine is routinely administered. The PCV is administered

at 2, 4, 6, and 12-15 months of age and a catch-up schedule should be established for all children younger than 5 years of age.[16] Children over 5 years of age who have not yet received the PCV series should be considered for vaccination, especially those with underlying chronic diseases such as SCD. PCV includes the pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F which have been associated with increasing penicillin-resistance. With regard to patients with SCD, Halasa and colleagues[30] evaluated the incidence of invasive pneuomcooccal disease before and after the introduction of PCV. Using the Tennessee Medicaid system, 2026 children with SCD were retrospectively identified from January 1995 through December 2004. Thirty-seven children developed invasive pneumococcal disease during this period with 21 of these children being less than 5 years of age. In comparing the incidence of invasive pneumococcal disease before (1995-1999) and after (2001-2004) the addition of the PCV, a statistically significant reduction in cases were observed, a decrease of 90.8% in children less than 2 years of age ($p<0.001$) and a decrease of 93.4% in children less than 5 years of age ($p<0.001$). A decrease in the number of invasive pneumococcal disease or cases in children greater than 5 years of age was also observed but was not statistically significant (from 161 cases per 100,000 person-years to 99 cases per 100,000 person years, $p=0.36$) Despite the impact of the PCV, children with SCD should still receive PPSV to protect against additional pneumococcal strains.[31]

CONCLUSIONS

Children with SCD have an increased susceptibility to bacterial infections, especially to those caused by *Streptococcus pneumoniae*. Pneumococcal vaccination and daily oral administration of penicillin V have significantly reduced the mortality associated with pneumococcal infection in these children. It is recommended that all children younger than 5 years with SCD take daily prophylactic antibiotics. All newborns screened for SCD and those who test positive should be started on prophylactic penicillin as early as possible. Children less than 5 years of age should receive oral penicillin 125 mg twice daily, and the dose should be increased to 250 mg twice daily for children older than 5 years. Amoxicillin 20 mg/kg/day is an alterative to penicillin. Penicillin-allergic patients may be given erythromycin 125 mg twice daily (less than 5 years of age) or 250 mg twice daily (greater than or equal to 5 years of age).

Children with recurrent invasive pneumococcal infections should receive penicillin prophylaxis indefinitely. At this time it is not known if penicillin prophylaxis is warranted in children over the age of five years. Children over the age of five years may be considered for discontinuation of penicillin prophylaxis who have received the PCV and PPSV, have previously received prolonged periods of pencillin prophylaxis, are under the regular supervision of a medical practioner, do not have a history of severe pneumococcal infection, or have not had functional/surgical splenectomy.[16] Although penicillin prophylaxis has significantly decreased the rate of *S. pneumoniae* colonization in those with SCD, it may also increase the risk of selective colonization with penicillin-resistant *S. pneumoniae*.

Education for families of children with sickle cell disease is paramount to the successful management of a child with SCD. As with many diseases, compliance with antibiotic therapy is highly variable and can be problematic. All practitioners should stress the importance of compliance with penicillin prophylaxis. Parents should be instructed to diligently look for any signs or symptoms of febrile illness and should aggressively seek medical attention for all such events.

The importance of maintaining the recommended pediatric immunization schedule, including the pneumococcal conjugate vaccine (PCV), is important for all children but particularly for children with SCD. Since the addition of PCV in 2000, the incidence of invasive pneumococcal disease has continued to decrease among children with SCD less than 5 years of age.

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REFERENCES

1. Davies SC, Brozovic M. The presentation, management and prophylaxis of sickle cell disease. Blood Rev 1989;3:29-44.
2. Consensus conference. Newborn screening for sickle cell disease and other hemoglobinopathies. JAMA 1987;258:1205-1209.
3. Wethers DL. Sickle cell disease in childhood: Part I. Laboratory diagnosis, pathophysiology and health maintenance. Am Fam Physician 2000;62:1013-1020,1027-1028.
4. Okpala I, Thomas V, Westerdale N, et al. The comprehensive care of sickle cell disease. Eur J Haematol 2002;68:157-162.
5. Ohene-Frempong K. "Sickle Cell Diseases." Rudolph's Pediatrics. 21st ed.: 2003, 1531-1534.
6. Fixler J, Styles L. Sickle cell disease. Pediatr Clin North Am 2002;49:1193-1210.
7. DeBaun MR. Sickle Cell Disease. Kliegman RM, ed. Nelson Textbook of Pediatrics. 18th ed. Philadelphia, PA : Saunders; 2007.
8. Pai VB, Nahata MC. Duration of penicillin prophylaxis in sickle cell anemia: issues and controversies. Pharmacotherapy 2000;20:110-117.
9. Pearson HA. Prevention of pneumococcal disease in sickle cell anemia. J Pediatr 1996;129:788-789.
10. Zarowsky HS, Gallagher D, Gill FM, et al. Bacteremia in sickle hemoglobinopathies. J Pediatr 1986;109:579-585.
11. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. N Engl J Med 1986;314:1593-1599.
12. Hord J, Byrd R, Stowe L, et al. *Streptococcus pneumoniae* sepsis and meningitis during the penicillin prophylaxis era in children with sickle cell disease. J Pediatr Hematol Oncol 2002;246:470-472.
13. Zimmerman RK. Pneumococcal conjugate vaccine for young children. Am Fam Physician 2001;63:1991-1998.
14. [No author listed] Penicillin prophylaxis for babies with sickle-cell disease. Lancet 1986 Dec 20-27;2(8521-22):1432-1433.
15. National Institutes of Health. "Infection." Management and therapy of sickle cell disease. 3rd ed.: 1995, 29-33.
16. American Academy of Pediatrics. "Immunization in special clinical circumstances." Pickering LK, ed. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009..
17. Buchanan GR, Siegel JD, Smith SJ, DePasse BM. Oral penicillin prophylaxis in children with impaired splenic function: a study of compliance. Pediatrics 1982;70:926-930.
18. Knight-Madden J, Sergeant GR. Invasive pneumococcal disease in homozygous sickle cell disease: Jamaican experience 1973-1997. J Pediatr 2001;138:65-70.
19. Falletta JM, Woods GM, Verter JI, et al. Discontinuing penicillin prophylaxis in children with sickle cell anemia. J Pediatr 995;12:685-690.
20. Buchanan GR, Smith SJ. Pneumococcal septicemia despite pneumococcal vaccine and prescription of penicillin prophylaxis in children with sickle cell anemia. Am J Dis Child 1986;140:428-432.
21. Anglin DL, Siegel JD, Pacini DL, et al. Effect of penicillin prophylaxis on nasopharyngeal colonization with *Streptococcus pneumoniae* in children with sickle cell anemia. J Pediatr 1984;104:18-22.
22. Berkovitch M, Papadouris D, Shaw D, et al. Trying to improve compliance with prophylactic penicillin therapy in children with sickle cell disease. Br J Clin Pharmacol 1998;45:605-607.
23. Teach SJ, Lillis KA, Grossi M. Compliance with penicillin prophylaxis in patients with sickle cell disease. Arch Pediatr Adolesc Med 1998;152:274-278.
24. Mahat G, Scoloveno MA, Donnelly CB. Written educational materials for families of chronically ill children. J Am Acad Nurse Pract 2007;19:471-6.
25. Bjornson AB, Falletta JM, Verter JI, et al. Serotype-specific immunoglobulin G antibody responses to pneumococcal polysaccharide vaccine in children with sickle cell anemia: effects of continued penicillin prophylaxis. J Pediatr 1996;129:828-835.
26. Steele RW, Warrier R, Unkel PJ, et al. Colonization with antibiotic-resistant *Streptococcus pneumoniae* in children with sickle cell disease. J Pediatr 1996;128:531-535.

27. Norris CF, Mahannah SR, Smith-Whitley K, et al. Pneumococcal colonization in children with sickle cell disease. J Pediatr 1996;129:821-827.
28. Chesney PJ, Wilimas JA, Presbury G, et al. Penicillin- and cephalosporin-resistant strains of *Streptococcus pneumoniae* causing sepsis and meningitis in children with sickle cell disease. J Pediatr 1995;127:526-532.
29. Redding-Lallinger R, Knoll C. Sickle cell disease – pathophysiology and treatment. Curr Probl Pediatr Adolesc Health Care 2006;36:346-376.
30. Halasa NB, Shankar SM, Talbot TR, et al. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of pneumococcal conjugate vaccine. Clin Infect Dis 2007;44:1428-1433.
31. Adamkiewicz TV, Sarnaik S, Buchanan GR, et al. Invasive pneumococcal infections in children with sickle cell disease in the era of penicillin prophylaxis, antibiotic resistance, and 23-valent pneumococcal polysaccharide vaccination. J Pediatr 2003;143:438-444.