Nasopharyngeal Carriage of Penicillin-resistant *Streptococcus pneumoniae* in Children With Sickle Cell Disease

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**ABSTRACT.** *Objective.* We studied the prevalence of nasopharyngeal (NP) carriage, antimicrobial susceptibilities, and serotypes of *Streptococcus pneumoniae* (SP) in children with sickle cell disease (SCD) in the Mid-South. In addition, we examined risk factors for NP carriage of penicillin-resistant SP (PRSP).

*Study Design.* Between July 1994 and December 1995, we obtained NP cultures from 312 children with SCD followed at the Mid-South Sickle Cell Center, 208 (67%) of whom were receiving penicillin prophylaxis.

*Results.* Among the 312 patients, colonization with SP occurred in 42 (13%), 30 (71%) of whom were receiving penicillin prophylaxis. Twenty-three of the 42 SP isolates (55%) were resistant to penicillin; 5 of the 23 (22%) were highly resistant. PRSP organisms were also resistant to cefotaxime (43%), trimethoprim-sulfamethoxazole (57%), and erythromycin (22%). Serotypes 6A, 6B, 14, 19A, and 23F accounted for 19 (90%) of 21 resistant strains. Children who were treated with antibiotics during the preceding month were more likely to carry PRSP than children who were not treated.

*Conclusions.* There is a high prevalence of NP carriage of PRSP in children with SCD in the Mid-South, which raises concerns regarding the continued effectiveness of penicillin prophylaxis in these children. Further studies on the antimicrobial susceptibilities of resistant organisms and the relationship between NP carriage of SP and invasive disease are needed before developing new recommendations for prophylaxis and treatment. *Pediatrics* 1997;99(4). URL: [http://www.pediatrics.org/cgi/content/full/99/4/e7](http://www.pediatrics.org/cgi/content/full/99/4/e7)

**Abbreviations.** SP, *Streptococcus pneumoniae*; SCD, sickle cell disease; NP, nasopharyngeal; PRSP, penicillin-resistant *S. pneumoniae*; MSSCC, Mid-South Sickle Cell Center; HbS, sickle cell hemoglobin; LBCM, LeBonheur Children’s Medical Center; MIC, minimal inhibitory concentration; E-test, epsilometric test; TMP-SMZ, trimethoprim-sulfamethoxazole; HR, high-level resistance; IR, intermediate-level resistance; CI, confidence interval.

*Streptococcus pneumoniae* (SP) is the most common cause of serious bacterial infections in children with sickle cell disease (SCD). Routine prophylactic use of oral penicillin has dramatically decreased the incidence of severe invasive pneumococcal infections.1 Recently, the prevalence of penicillin-resistant strains of SP has increased, and most of these strains also have decreased susceptibility to other antimicrobial agents, including the broad-spectrum cephalosporins.2–7 Worldwide, antimicrobial resistance has been associated with four serotypes, 6, 14, 19, and 23.8 Widespread use of penicillin,9 previous antibiotic use,10–12 day care center attendance,13,14 prior hospitalization,10,15 and young age11 have been implicated as risk factors for infection or colonization with antibiotic-resistant strains of SP in individuals without SCD.

The prevalence of nasopharyngeal (NP) carriage of SP in children with SCD has varied among studies, with an increased rate of penicillin-resistant organisms being recently observed.16–20 A high prevalence of NP carriage of antibiotic-resistant SP has been found in healthy children with otitis media in Memphis.21 Similarly, a high prevalence of penicillin- and cefotaxime-resistant strains of SP has been found among isolates from invasive infections in this area.22 Episodes of invasive disease caused by penicillin-resistant SP (PRSP) have been documented in children with SCD in the Mid-South as well as other parts of the United States.23,24

We conducted the present study to determine the prevalence of NP carriage, antimicrobial susceptibilities, and serotypes of SP in children with SCD who were followed at the Mid-South Sickle Cell Center (MSSCC). We also examined potential risk factors for NP carriage of penicillin-resistant SP.

**METHODS**

*Study Population.* The study population comprised children with SCD (sickle cell hemoglobin [HbS]S, HbSC, or HbS-thalassemia) followed at the MSSCC. The MSSCC in Memphis provides comprehensive care for approximately 600 children and adolescents with sickle cell hemoglobinopathies. Most patients reside in western Tennessee, northern Mississippi, and eastern Arkansas and receive their medical care at Le Bonheur Children’s Medical Center (LBCM). Penicillin prophylaxis is routinely started at 3 months and continued until at least 5 years of age. Twenty-three-valent pneumococcal vaccine is administered at 2 years of age with a booster given at 5 years of age. Eligible patients with SCD, evaluated in the clinic or LBCM emergency department between July 1994 and December 1995, were enrolled on the study. A small percentage (estimated at 15% to 20%) of these patients were not entered in the study because of parent and/or patient refusal or because they were missed during a busy clinic or emergency department day.

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study population was divided into two groups according to clinical status at time of enrollment. Group 1 comprised children evaluated during a routine clinic visit, and Group 2 consisted of children evaluated during an episode of fever and/or respiratory illness.

Procedure

Children were enrolled in the study after informed consent was obtained from the parent and/or patient as appropriate. Information regarding penicillin prophylaxis was recorded. An NP culture was obtained at enrollment either during a routine clinic visit or during an episode of fever and/or respiratory illness. NP cultures were collected from the nasopharynx using cotton-tipped flexible wire swabs inserted through the nostril in most children and from high in the oropharynx in a few children older than 10 years.

After a preliminary analysis, the importance of identifying risk factors for penicillin resistance became clear. Therefore, information regarding day care center attendance and antibiotic therapy during the preceding month was obtained from the subsequently enrolled patients. For those patients who were found to be colonized with SP, information regarding hospitalization during the preceding year was collected retrospectively.

Microbiologic Analysis

In the LBCMC microbiology laboratory, swabs were used to inoculate sheep blood agar plates within 3 hours of collection, and the plates were incubated for 48 hours in a 5% carbon dioxide environment. SP organisms were identified based on colony morphology with confirmation using Optochin (ethyl hydrocuprein HCl) discs. The strains were then screened for penicillin susceptibility using Mueller-Hinton agar plates with sheep blood and 1 μg of oxacillin Kirby-Bauer susceptibility discs. A zone of inhibition of less than 20 mm indicated potential penicillin resistance. Quantitative susceptibilities of putative penicillin-resistant strains were then determined using the epiisolometric test (E-test; AB Biodisk, Solna, Sweden) strips. The E-test is a method for determining minimum inhibitory concentration (MIC) based on the diffusion of an antibiotic gradient from a plastic strip onto inoculated agar media. The PRSP strains were further tested for susceptibilities to cefotaxime using the E-test, and to erythromycin and trimethoprim-sulfamethoxazole (TMP-SMZ) using Kirby-Bauer susceptibility discs. Levels of resistance were defined according to the National Committee for Clinical Laboratory Standards guidelines: high-level resistance (HR) to penicillin, MIC, greater than 1.0 μg/ml; intermediate-level resistance (IR) to penicillin, MIC, 0.1 to 1.0 μg/ml; HR to cefotaxime, MIC, 2.0 μg/ml or greater; and IR to cefotaxime, MIC, 1.0 μg/ml. All isolates were frozen in trypticase soy broth with 20% glycerol at −70°C for transport to the Centers for Disease Control and Prevention. Serotypes of SP isolates were determined at the Centers for Disease Control and Prevention by the Danish Neufeld-Quellung reaction with pooled streptococcal antisera.

Statistical Considerations

The relationships between both NP carriage of SP and NP carriage of penicillin-resistant SP and season when enrolled, age at enrollment, type of SCD, acute illness, use of penicillin prophylaxis, recent antibiotic therapy, and day care center attendance were examined by univariate analysis in the total patient population using the logistic regression model. The risk factors identified by univariate analysis (P ≤ .2) were further examined by multivariate analysis using a multiple logistic regression model, which included only those patients for whom information regarding all the identified risk factors was available. In the subset of patients who were colonized with SP, the relationships between NP carriage of penicillin-resistant SP and each of the above potential risk factors as well as prior hospitalization were studied by univariate analysis using the exact logistic regression model. The exact logistic regression model was used instead of the logistic regression model in this subset because of the small sample size. Because only younger children were at risk of day care exposure, analyses of the relationships to this particular factor were performed only in children younger than 6 years.

RESULTS

Patient Characteristics

During an 18-month period (July 1994 to December 1995), 312 patients with SCD (HbSS, n = 195; HbSC, n = 93; and HbSβ-thalassemia, n = 24) were enrolled on the study. All patients were African-American. There were 171 male and 141 female patients; they ranged in age from 2 weeks to 18.2 years (median, 4.3 years). Group 1 comprised 267 patients (86%), and Group 2 contained 45 patients (14%). Of the 312 enrollees, 208 (67%) were receiving penicillin prophylaxis. As expected, significantly more children aged 5 years and younger were receiving penicillin prophylaxis (83%) than children older than 5 years (47%) (P < .001, χ² test). Twenty-three (12%) of the 194 patients for whom information was available had received antibiotic therapy other than penicillin prophylaxis during the preceding month. Of the 216 children for whom information was available, 28 (ages 4 months to 5.4 years) attended day care centers.

Pneumococcal Carriage and Resistance to Antibiotics

Of the 312 patients enrolled in the study, 42 (13%) were colonized with SP (Table 1). Twenty-three of the 42 SP isolates (55%) were resistant to penicillin (MIC, 0.1 to 8.0 μg/ml); 18 (78%) were of intermediate resistance; and 5 (22%) were highly resistant. Of the 23 isolates resistant to penicillin, 19 (83%) were obtained from patients receiving penicillin prophylaxis. The relationships of NP carriage of SP and PRSP to penicillin prophylaxis are displayed in Fig 1. PRSP isolates also had resistance to other antibiotics. Ten organisms (43%) were resistant to cefotaxime (MIC, 1.0 to 8.0 μg/ml); 4 were IR, and 6 were HR. Thirteen of 23 (57%) PRSP isolates were resistant to TMP-SMZ, and 5 (22%) were resistant to erythromycin.

Pneumococcal NP Carriage and Season

During the 18-month period of the study, 21 (20%) of the 105 cultures collected in December through February and 5 (17%) of 29 cultures collected in March through May grew SP. In contrast, only 7 (8%) of the 83 cultures collected in June through August and 9 (9%) of 95 cultures collected in September through November were positive for SP (Fig 2). Children carried SP in their nasopharynx 2.4 times more often during the winter and spring (December through May) than during the summer and fall (June

<table>
<thead>
<tr>
<th>TABLE 1. Nasopharyngeal Carriage of Streptococcus pneumoniae (SP) in Children With Sickle Cell Disease</th>
<th>No. of Patients</th>
<th>No. of Patients With Colonization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1*</td>
<td>267</td>
<td>34</td>
</tr>
<tr>
<td>Group 2†</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>312</td>
<td>42</td>
</tr>
</tbody>
</table>

* Children evaluated during routine clinic visits.
† Children with fever and/or respiratory illness.
through November) (95% confidence interval [CI], 1.2 to 4.8; \( P = .009 \)).

**Serotype Data**

The serotypes of 36 SP isolates, including 21 PRSP isolates, were determined. Serotypes 6A, 6B, 14, 19A, and 23F accounted for 25 (69%) of the 36 SP strains and 19 (90%) of the 21 resistant strains (Table 2).

**Risk Factors**

In the univariate analysis of the potential risk factors for NP carriage of SP, only age and recent antibiotic therapy were found to be significant (\( P = .027 \) and .050, respectively) (Table 3). These factors also proved to be significant by multivariate analysis, which included only the 194 patients for whom information regarding recent antibiotic therapy was available. Young children (18 months and younger) were 2.5 times more likely to carry SP in their nasopharynx than those older than 18 months (95% CI, 1.1 to 5.6). Children who received antibiotic therapy during the preceding month were 2.6 times more likely to be colonized with SP than those who did not (95% CI, 0.9 to 7.1). No significant interaction was found between age and recent antibiotic therapy.

In the univariate analysis of potential risk factors for NP carriage of penicillin-resistant SP, recent antibiotic therapy was found to be significant (\( P = .006 \)), and age was of borderline significance (\( P = .057 \)) (Table 3). In addition, 19 (9%) of 208 patients receiving penicillin prophylaxis grew PRSP, whereas 4 (4%) of 103 patients not receiving penicillin prophylaxis grew PRSP (\( P = .1 \)). Recent antibiotic therapy, age, and penicillin prophylaxis were examined by multivariate analysis of the 194 patients for whom information regarding antibiotic therapy was available. Children treated with antibiotics during the preceding month were 4.6 times more likely to carry PRSP than those who were not treated (95% CI, 1.5 to 14.0). Young children (18 months and younger) were 2.6 times more likely to carry PRSP than children older than 18 months (95% CI, 0.9 to 7.1). The relationship between NP carriage of PRSP and penicillin prophylaxis as well as the interactions among the three studied factors were not significant.

To determine whether any of the potential risk factors, including multiple hospitalizations, could be predictive of penicillin resistance once the patient was colonized, a univariate analysis of these factors was performed in the 42 patients who were colonized with SP (Table 4). Although no risk factor significantly predicted that the carried organism was penicillin resistant, the percentage of patients receiving penicillin prophylaxis who carried PRSP was almost double the percentage of patients not receiving penicillin prophylaxis (63% vs 33%). Similarly, the percentage of patients recently treated with antibiotics who carried PRSP was about 1.7 times greater than the percentage of patients not recently treated with antibiotics (86% vs 50%).

**DISCUSSION**

SP strains that colonize the nasopharynx may be associated with invasive disease.\(^2\) NP carriage occurs in about one third of healthy children, with infants having the highest rate.\(^2\) From a study conducted in Memphis from May through September 1993, the Centers for Disease Control and Prevention reported that 30% of NP cultures obtained from healthy children with otitis media grew SP. Between July 1994 and December 1995, we found that 13% of children with SCD followed at the MSSCC were colonized with SP. This prevalence was lower than that found in healthy children but similar to the NP carriage rates reported in children with SCD by Overturf et al (17.8%).\(^1\) Anglin et al

![Fig 1.](http://www.pediatrics.org/cgi/content/full/99/4/e7)
and Steele et al (12%). Furthermore, the study by Anglin et al\textsuperscript{17} showed that the prevalence of carriage in children with sickle cell anemia who were receiving penicillin prophylaxis was significantly lower than that of control children (34.4%), particularly during the winter months. In our study, the lower rate of NP carriage among children with SCD compared with that in healthy children did not seem to be related to the use of penicillin prophylaxis, because the rates of carriage were similar in patients receiving penicillin prophylaxis and those not receiving penicillin prophylaxis (Table 3). Our inability to show an effect of penicillin prophylaxis may be related in part to age differences between the groups, because more young children, who are at a higher risk to be colonized with SP, were also receiving penicillin prophylaxis. Other studies have reported even lower rates of pneumococcal NP carriage in children with SCD. In a study from Cleveland,\textsuperscript{18} 6.2% of children with SCD who had cultures taken between December 1990 and March 1991 were colonized with SP. However, this colonization rate was similar to that (5.1%) of the control group of healthy children. In addition, the collaborative, multicenter Ancillary Nasopharyngeal Culture Study, performed in sickle cell patients followed for 3 years, showed the overall rate of NP carriage of SP to be 5.5%.\textsuperscript{19} Discrepancies among colonization prevalence figures may be related in part to differences in children’s ages, methods of collection, and time to inoculation of specimens.

During the past two to three decades, SP resistance

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**TABLE 3.** Univariate Analyses of Risk Factors for Nasopharyngeal Carriage of *Streptococcus pneumoniae* (SP) and Penicillin-resistant SP (PRSP) in Patients With Sickle Cell Disease

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total No.</th>
<th>No. Colonized With SP (%)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
<th>No. Colonized With PRSP (%)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>82</td>
<td>17 (21)</td>
<td>2.1 (1.1–4.2)</td>
<td>.027</td>
<td>10 (12)</td>
<td>2.3 (1.0–5.5)</td>
<td>.057</td>
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<tr>
<td>&gt;18</td>
<td>230</td>
<td>25 (11)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hemoglobinopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SS</td>
<td>195</td>
<td>27 (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC</td>
<td>93</td>
<td>14 (15)</td>
<td></td>
<td></td>
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<tr>
<td>S-β-thalassemia</td>
<td>24</td>
<td>1 (4)</td>
<td>*</td>
<td>.37</td>
<td>0 (0)</td>
<td>*</td>
<td>.28</td>
</tr>
<tr>
<td>Acute illness</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45</td>
<td>8 (18)</td>
<td>1.5 (0.6–3.5)</td>
<td>.36</td>
<td>5 (11)</td>
<td>1.7 (0.6–4.9)</td>
<td>.30</td>
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<tr>
<td>No</td>
<td>267</td>
<td>34 (13)</td>
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<td>Penicillin prophylaxis</td>
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<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>208</td>
<td>30 (14)</td>
<td>1.3 (0.6–2.7)</td>
<td>.46</td>
<td>19 (9)</td>
<td>2.5 (0.8–7.5)</td>
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<tr>
<td>No</td>
<td>103</td>
<td>12 (12)</td>
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<td>Antibiotic therapy during the previous month</td>
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<tr>
<td>Yes</td>
<td>23</td>
<td>7 (30)</td>
<td>2.7 (1.0–7.2)</td>
<td>.05</td>
<td>6 (26)</td>
<td>4.7 (1.6–14.1)</td>
<td>.006</td>
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<td>171</td>
<td>24 (14)</td>
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<td>Day care attendance†</td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>28</td>
<td>6 (21)</td>
<td>1.3 (0.5–3.7)</td>
<td>.61</td>
<td>4 (14)</td>
<td>1.4 (0.4–4.6)</td>
<td>.62</td>
</tr>
<tr>
<td>No</td>
<td>110</td>
<td>19 (17)</td>
<td></td>
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</tbody>
</table>

* An overall odds ratio could not be calculated because of the presence of three types of hemoglobinopathy.
† Only children younger than 6 years were included in the analyses.

**TABLE 4.** Univariate Analysis of Risk Factors for Nasopharyngeal Carriage of Penicillin-resistant *Streptococcus pneumoniae* (PRSP) in Patients With Sickle Cell Disease Colonized With SP

<table>
<thead>
<tr>
<th>Feature</th>
<th>No. of PRSP/No. of SP Isolates (%)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Age, mo</td>
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<td></td>
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<tr>
<td>&lt;18</td>
<td>10/17 (59)</td>
<td>1.3 (0.3–5.5)</td>
<td>.91</td>
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<td>&gt;18</td>
<td>13/25 (52)</td>
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<td>Hemoglobinopathy</td>
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<tr>
<td>SS</td>
<td>17/27 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SC</td>
<td>6/14 (43)</td>
<td>2.2 (0.5–10.4)</td>
<td>.37</td>
</tr>
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<td>Acute illness</td>
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<td></td>
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<tr>
<td>Yes</td>
<td>5/8 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18/34 (53)</td>
<td>1.5 (0.2–11.0)</td>
<td>.93</td>
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<td>Penicillin prophylaxis</td>
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<tr>
<td>Yes</td>
<td>19/30 (63)</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>4/12 (33)</td>
<td>3.4 (0.7–19.0)</td>
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<td>Antibiotic therapy during previous month</td>
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</tr>
<tr>
<td>Yes</td>
<td>6/7 (86)</td>
<td>5.7 (0.6–297.5)</td>
<td>.21</td>
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<tr>
<td>No</td>
<td>12/24 (50)</td>
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<td>Day care attendance†</td>
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<tr>
<td>Yes</td>
<td>4/6 (67)</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>12/19 (63)</td>
<td>1.2 (0.1–16.0)</td>
<td>1.00</td>
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<tr>
<td>Hospitalization during preceding 3 mo</td>
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</tr>
<tr>
<td>Yes</td>
<td>1/2 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22/40 (55)</td>
<td>0.8 (0.01–67.7)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Only patients younger than 6 years were included in the analysis.
to penicillin has become a global problem.\textsuperscript{29,30} In the United States, the prevalence has increased dramatically during the past 5 years and has been variable depending on the geographic area. Moreover, there has been a parallel rise of SP resistance to other antibiotics, including the broad-spectrum cephalosporins.\textsuperscript{4–6,31,32} To address this problem in children with SCD in the Mid-South, we determined the antimicrobial susceptibilities of SP isolated from the nasopharynx. Fifty-five percent of SP isolates were resistant to penicillin; this was substantially higher than the 29% observed in healthy children in this area 1 year earlier.\textsuperscript{21} Even more worrisome was the high rate of resistance to cefotaxime (43%) among PRSP, which included 26% with a high level of resistance. PRSP strains were also resistant to the commonly used oral antibiotics TMP-SMZ and erythromycin. Increased carriage of antibiotic-resistant SP creates the potential for an increased incidence of pneumococcal disease resulting from resistant strains and a major threat to children with SCD who are at increased risk for pneumococcal infections (400 times greater than in healthy children\textsuperscript{33}). In the past, management of these children has consisted of the use of penicillin prophylaxis, administration of pneumococcal vaccine (in children 2 and older), and treatment with broad-spectrum cephalosporins. The results of this study raise questions regarding the continued effectiveness of penicillin prophylaxis and the availability of alternative approaches.

Episodes of invasive infections caused by penicillin-resistant SP have been documented in children with SCD. In a previous review of cases of pneumococcal sepsis and meningitis in children with SCD followed by the MSSCC\textsuperscript{23} 4 (15%) of 26 episodes were caused by penicillin-resistant strains, 1 of which was also resistant to ceftriaxone and other antibiotics (multiply resistant). Two additional patients from the southeastern United States with resistant strains were identified, one of whom had a multiply resistant strain. Both patients with multiply resistant strains died. Identification of these children prompted us to modify our initial treatment of severely ill patients with SCD and suspected sepsis by adding vancomycin to ceftriaxone (or cefotaxime) pending results of cultures and antimicrobial susceptibilities. The criteria used to define “suspected sepsis” and the need for hospitalization included any one of the following: “toxic” appearance, temperature higher than 40°C, leukocyte count less than 5.0 × 10^9/L or more than 30.0 × 10^9/L, absolute neutrophil count less than 2.0 × 10^9/L, the presence of pulmonary infiltrates, and history of previous bacterial sepsis.\textsuperscript{34} Whether the occurrence of invasive disease caused by PRSP is related to the observed increased prevalence of colonization with resistant organisms remains to be determined.

Penicillin resistance in our study was associated with SP serotypes 6A, 6B, 14, 19A, and 23F. Serogroups 6, 14, 19, and 23 are the strains of SP most often carried by children and most often associated with antimicrobial resistance in all ages.\textsuperscript{8} Furthermore, these strains are poor immunogens in children younger than 2 years.\textsuperscript{35}

The incidence of pneumococcal NP carriage was highest in the winter and spring, consistent with the seasonal incidence of respiratory illnesses.\textsuperscript{28} Children younger than 18 months had significantly higher rates of NP carriage of SP than did older children. Our observation was similar to that made in healthy children by Zenni et al,\textsuperscript{36} who noted higher rates of SP colonization in younger children, with a peak at 1 year of age. Children with a history of antibiotic therapy during the preceding month were also significantly more likely to have been colonized with SP, perhaps because they were more likely to have had a respiratory illness. However, we observed no significant relationship between NP carriage of SP and acute illness in our study.

In healthy children, day care center attendance,\textsuperscript{13,14} the presence of siblings,\textsuperscript{14} antibiotic use,\textsuperscript{10–12} prior hospitalization,\textsuperscript{10,15} and young age\textsuperscript{11} have been associated with a higher risk for colonization or infection with PRSP. In a study of NP carriage of SP in healthy children in an Ohio day care center, Reichler et al\textsuperscript{11} found that the risk of carrying resistant SP organisms was related to frequent use of antibiotics during the preceding 3 months or prophylactic antimicrobial therapy during the preceding year. In children with sickle cell disease, a recent study from Louisiana\textsuperscript{20} showed that NP colonization with SP was associated with age younger than 2 years and day care attendance of more than 20 h/wk. Penicillin resistance was identified more frequently among isolates from patients with sickle cell disease, 93% of whom were receiving penicillin prophylaxis, than from healthy control subjects. This study, however, did not address the issue of penicillin resistance in relation to day care center attendance. In our study, penicillin resistance was significantly associated with recent antibiotic therapy but not with penicillin prophylaxis or day care center attendance (Tables 3 and 4). Although penicillin resistance seemed to occur more frequently among isolates from patients who were receiving penicillin prophylaxis than those who were not, the difference did not reach statistical significance. These findings should be interpreted with caution, especially because the power of our study to show significant associations was limited by the small sample size and the lack of a control group. Moreover, the low rate (20% of children aged 6 years and younger) of day care center attendance in our patient population and the absence of well-defined criteria for attendance may have contributed to our inability to relate penicillin resistance to day care center attendance.

From January 1, 1994, through December 30, 1994, 24% of SP organisms isolated from all blood, cerebrospinal fluid, and bone and joint specimens at LBCMC were resistant to penicillin.\textsuperscript{22} For cerebrospinal fluid isolates only, 38% were resistant to penicillin. Therefore, the high prevalence of NP carriage of PRSP in children with SCD in the Mid-South may very well reflect epidemiologic patterns seen in this
area. In a recent study of normal children with acute otitis media from rural Kentucky, where PRSP is highly prevalent, only an “otitis-prone” condition (three or more episodes of acute otitis media in the preceding 4 months) and the number of pretympanocentesis antibiotic courses were predictive of the presence of PRSP in middle ear fluid; age, day care center attendance, recent antibiotic therapy, antibiotic prophylaxis during the previous 3 months, and hospitalization were not significant factors.32

Although penicillin prophylaxis seems to decrease NP carriage of SP, other mechanisms may be involved in its demonstrated efficacy in the prevention of pneumococcal infections in children with SCD. Our findings that 13% of children with SCD, the majority of whom were receiving penicillin prophylaxis, were colonized with SP and that 55% of the organisms were resistant to penicillin suggest the possibility of increasing numbers of invasive disease caused by resistant organisms in these children. Studies designed to examine the relationship between NP colonization with SP and invasive disease are needed to delineate this problem further.

The initial treatment of suspected pneumococcal sepsis in children with SCD in the era of PRSP and multiply resistant SP is difficult and has been previously reviewed.23 The potential for the emergence of SP resistant to vancomycin, such as has recently de-veloped among enterococci,38 is of concern. Thus, the spread of multiply resistant Streptococcus pneumoniae at a day care center in Ohio. J Infect Dis. 1992;166:1346–1353

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