Duration of Rifampin Chemoprophylaxis for Contacts of Patients Infected with *Haemophilus influenzae* Type B

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Rifampin is recommended as a prophylactic treatment for intimate contacts of young children who develop invasive infections with *Haemophilus influenzae* type B (Hib). A 4-day course of rifampin (20 mg/kg of body weight per day, not to exceed 600 mg as a maximum single daily dose) is 95% effective in eradicating pharyngeal colonization with Hib, thus effectively reducing the risk of both associated patients and recurrent illness in index patients less than 2 years old. This study compares rates of eradication of pharyngeal colonization with Hib for 2- and 4-day courses of rifampin therapy. One hundred sixty-three patients with Hib infection were treated at Children's Hospital of Pittsburgh between January 1986 and December 1988; prophylaxis was recommended for 128. Participating families were randomized to receive either 2- or 4-day therapy. Throat swabs were obtained from contacts prior to therapy. Repeat cultures were obtained from colonized contacts 2 days after completing rifampin and again on all contacts 7 to 10 days after completing therapy. Of 68 participating families, 34 received 2-day and 34 received 4-day therapy with rifampin. Twenty-two of 24 colonized contacts in the 2-day group and 17 of 18 in the 4-day group had negative cultures for Hib on follow-up. Two-day therapy with rifampin appears to be as effective as 4-day treatment in the eradication of Hib pharyngeal colonization.

Rifampin is the only antimicrobial agent consistently effective in eradicating pharyngeal colonization with *Haemophilus influenzae* type b (Hib) (10). As a chemoprophylactic agent, limited data suggest that it is effective in reducing the occurrence of subsequent cases of Hib disease among household and day-care contacts of children with invasive Hib disease (1, 6). Although active immunization is the most important element in efforts to eliminate Hib disease, chemoprophylaxis with rifampin will remain an important preventive strategy in particular situations.

The recommended dosage of rifampin for prophylaxis against Hib is 20 mg/kg of body weight orally once daily for 4 days; this regimen results in a 95% eradication of pharyngeal colonization with Hib (8, 9, 11, 14, 16). This study compares 2- and 4-day rifampin therapy in eradicating pharyngeal colonization with Hib in contacts of patients with invasive Hib disease.

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MATERIALS AND METHODS

All patients admitted to Children's Hospital of Pittsburgh with the diagnosis of invasive Hib infection between January 1986 and December 1988 were identified by a daily review of logs maintained by the microbiology laboratory. The diagnosis of Hib infection required the recovery of Hib in culture of a specimen from a normally sterile body fluid or site. Prophylaxis was recommended if the index patient either was less than 24 months of age or had close contact with age-susceptible children (those 48 months of age or younger) at home or in day-care. Individuals with at least 20 h of exposure to the index patient in the week preceding hospitalization were considered to be close contacts and were eligible for enrollment in the study after informed consent was obtained.

Throat cultures were obtained from close contacts who consented to participate in the study and were immediately inoculated on modified Hib agar (14) (burro antiserum was kindly provided by J. B. Robbins). Cultures were incubated at 35°C in 5% CO₂ and examined for halo-forming colonies after 1 and 2 days. Halo-forming colonies were confirmed to be Hib by standard microbiologic methods. All eligible contacts of a given index patient were managed similarly and were randomly assigned to receive either 2- or 4-day therapy with rifampin in a single daily oral dose. Individuals weighing over 40 lb (1 lb = 0.45 kg) were given 600 mg/day. Children weighing between 20 and 40 lb were given 300 mg/day. Infants weighing less than 20 lb were given approximately one-half of a 300-mg capsule per day. Although these dosages are approximations of those recommended by the American Academy of Pediatrics, they were chosen because of ease of administration and availability and have been used successfully in our previous studies. Children were medicated by placing the contents of a capsule(s) onto a teaspoon containing a semisolid food vehicle (e.g., applesauce). The medication was kindly supplied by the Allegheny County Health Department.

A repeat throat culture was obtained from each contact with an initially positive culture 2 to 3 days after rifampin therapy was completed and from all contacts 7 to 10 days after completion of rifampin therapy. Pharyngeal colonization was considered to have been eradicated if both follow-up cultures were negative for Hib. Colonization was considered to have been acquired if a follow-up culture was positive for Hib after an initially negative culture.

Two hundred eighty-three eligible contacts within the 68 participating family units were identified. Rifampin was distributed to these contacts at the time of the initial throat culture, usually within the first few days of hospitalization of the index patient. Whenever possible, all contacts within a

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family unit were cultured and treated simultaneously or within 1 day. At the time of follow-up cultures, family members were questioned concerning completion of their rifampin, as well as discoloration of urine and other body fluids as a measure of compliance and absorption of rifampin.

Statistical analysis. Comparisons of rates were determined by the chi-square test or, when appropriate, by the Fisher exact test. Confidence intervals for proportions were determined in a standard fashion (2).

RESULTS

During the study period, 163 patients were hospitalized with invasive Hib infections, including 61 with meningitis, 34 with epiglottitis, 31 with cellulitis, 15 with sepsis, 10 with pneumonia, 8 with septic arthritis, 2 with pericarditis, and 2 with peritonitis. Prophylaxis with rifampin was recommended for contacts of 128 index patients. Sixty-eight family units agreed to participate in the study; 34 received 2-day and 34 received 4-day therapy with rifampin. Most families that declined entry into the study lived outside the greater Pittsburgh area.

Forty-six of 287 (16%) eligible contacts were colonized with Hib. The majority (76%) of positive contacts were siblings less than 12 years of age. The rate of colonization among siblings less than 12 years of age differed significantly from similarly aged, nonsibling contacts (34 of 70 versus 2 of 37; $P < 0.001$). The rate of colonization was similar for siblings less than 6 and for those between 6 and 12 years of age (21 of 40 versus 13 of 30; $P = 0.60$). Neither of the two siblings older than 12 years of age was colonized with Hib. However, a 16-year-old baby sitter and a 14-year-old neighbor were colonized. The rate of pharyngeal colonization for parents was 6% and was not different for mothers or fathers (4 of 68 versus 3 of 54; $P = 0.63$). The only other colonized adult was a grandmother who had been a houseguest for several weeks in the home of a child with meningitis. The remaining 54 adults identified as close contacts had negative cultures.

Thirty-six of the index patients had no intimate contacts positive for Hib. In 10 of these, the index patient attended day-care. Additionally, a 22-month-old neighbor of an 11-month-old child with meningitis was hospitalized with Hib bacteremia 24 h after the admission of the 11-month-old child. These most likely represent coprimary cases; no other intimate contact was found in either family.

Table 1 shows that the rates of clearance of pharyngeal colonization with Hib in the two treatment groups did not differ significantly. Two of the 24 positive contacts treated in the 2-day group and 1 of 18 contacts in the 4-day group had positive cultures at the time of follow-up testing; 3 additional positive contacts in the 4-day group did not return for follow-up. In one case of treatment failure in the 2-day group the contact had taken only a single dose of medication. In the remaining two treatment failures compliance was judged to be good. Each persistently positive contact was retreated with a 4-day course of rifampin; all follow-up cultures were negative.

One child, a 5-year-old contact of an infant with meningitis, treated in the 2-day group, was found to have a positive culture for Hib on follow-up testing, although his initial culture was negative. Sensitivity testing of the isolate, performed after several subsequent treatment failures with 4-day rifampin therapy, showed resistance to rifampin (MIC, >8 $\mu$g/ml). The original isolate was not available for susceptibility testing. Two-day rifampin therapy was successful in eradicating Hib pharyngeal colonization in the father of this infant.

DISCUSSION

Rifampin prophylaxis is recommended for all household contacts of children with invasive Hib disease, in those households with at least one contact younger than 48 months of age (11). We have extended these recommendations to include those households in which the age of the index patient is less than 2 years, even when there are no other child contacts, because of the risk of recurrent infection in index children who are too young to reliably develop immunity after their Hib infection (12). The currently recommended dosage of 20 mg of rifampin per kg once daily has been found to be 95% effective in eradicating Hib in close contacts with Hib. Previous evaluations of 2-day therapy with rifampin employed a dose of 10 mg/kg given either daily (17) or twice daily (5) in contrast to the single daily dose of approximately 20 mg/kg used in the current study. In both of these earlier studies the effectiveness was considered unsatisfactory, probably attributable to a lower peak level of antibiotic.

The rates of clearance of pharyngeal colonization were similar in our two treatment groups and did not vary with age. Because of the lack of a rifampin suspension, the dose utilized in both treatment arms of this study did not strictly adhere to the recommended 20 mg/kg/day dose. However, the dosing regimen used, based upon weight, is the same as in our previous report (14). This regimen was not associated with toxicity in this or our previous study.

Two-day therapy offers several advantages over the current 4-day regimen. A recent cost-benefit analysis of rifampin prophylaxis estimated an average cost per household of $100 for 4-day therapy (12). The use of 2-day therapy should result in a substantial savings per family. This reduction in cost (13), along with the decreased duration of treatment (7), are likely to lead to enhanced compliance among contacts. Finally, the knowledge of the efficacy of 2-day therapy should reassure clinicians concerned about patients who miss one or two doses when the 4-day regimen is prescribed.

The rate of pharyngeal colonization with Hib among siblings of index patients within this study was 45%; Michaels and Norden reported a rate of 68% (15). Only a few

<table>
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<th>Characteristic</th>
<th>Therapy</th>
<th>2-Day</th>
<th>4-Day</th>
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<tr>
<td>No. of family units</td>
<td>34</td>
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<td>No. of significant contacts</td>
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<tr>
<td>Other</td>
<td>57</td>
<td>34</td>
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<tr>
<td>No. of positive contacts</td>
<td>24</td>
<td>21*</td>
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<tr>
<td>Rate of clearance of pharyngeal colonization</td>
<td>22/24 (92)</td>
<td>17/18 (94)</td>
<td></td>
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<td>95% Confidence interval (%)</td>
<td>73–99</td>
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* Three contacts with positive pharyngeal cultures for Hib did not return for follow-up cultures.

$^a$ Number of contacts with negative cultures at both 2- or 3-day and 10-day follow-up divided by number of initial cultures positive for Hib.
of the parents of index patients in our study group were colonized with Hib. The 6% rate for both fathers and mothers differs from rates of 3 and 20%, respectively, reported previously (15). The differences in frequencies of maternal (6 versus 20%) and sibling colonization (45 versus 68%; P < 0.01) observed here and previously may be explained in part by attendance in day-care, which leads to fewer contact hours within a household setting. The increased number of mothers who work outside the home and the increased participation of fathers in parenting may also account for the equal and low rates of colonization with Hib in parents of index patients.

Although 2-day therapy appears as effective as 4-day therapy in eradicating pharyngeal colonization with Hib, the statistical power of this study is limited. In order to obtain an 80% power, it would have been necessary to have several hundred positive contacts in each treatment group. The identical confidence intervals for the success rate for each treatment group, however, support the validity of our findings. The difficulty in conducting such a study is underscored by the fact that this is the only randomized comparative trial evaluating the efficacy of rifampin in the eradication of pharyngeal colonization with Hib. The number of colonized contacts treated with 2-day therapy in this study is equal to or greater than the vast majority of previously published evaluations of 4-day therapy. Similar investigations at other centers will be necessary to confirm our findings, although the decrease in cases of Hib disease since the introduction of conjugate vaccines may make such studies impossible. Currently, we are providing 2-day rifampin therapy in an open, nonrandomized trial to index patients and their close contacts. We continue to obtain throat cultures before and after treatment. Under this protocol we have successfully treated six additional colonized contacts with 2-day therapy, raising the success rate to 93% (28 of 30; 95% confidence interval, 78 to 99%). We have also successfully eradicated colonization in seven of eight index cases treated with 2-day therapy.

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REFERENCES


