Group A Streptococcus Carriage among Close Contacts of Patients with Invasive Infections

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During the past few years, the incidence of invasive group A Streptococcus (GAS) infection has been increasing. However, there are presently no clear recommendations regarding antibiotic prophylaxis for close contacts of index patients. The aims of this study were 1) to determine the prevalence of carriage of the same GAS strain as the patient's among contacts of patients with invasive infections and 2) to assess the importance of exposure duration. From March 1995 to March 1996, the authors prospectively included in the study all patients with invasive GAS infection, as defined by the Working Group on Severe Streptococcal Infections, who came to Hôpital Maisonneuve-Rosemont in Montreal, Quebec, Canada. An epidemiologic investigation was systematically carried out for each index case. Contacts were divided into two groups: those who had spent 24 hours or more with the index patient during the week preceding the beginning of his or her illness and those who had spent 12–24 hours with the index patient during that week. Strains of GAS were examined by serotyping (proteins M and T and the presence or absence of the serum opacity factor) and by characterization of streptococcal pyrogenic exotoxins (exotoxins A, B, and C). One hundred and two contacts of 17 index cases with invasive GAS infection were systematically screened. Contacts were considered positive if they carried the same strain of the bacterium and the same streptococcal pyrogenic exotoxin as the index case. Among the contacts who had spent at least 24 hours per week with their respective index cases, 13 out of 48 (27%) were found to be harboring the same serotype of GAS as the index patient (95% confidence interval 14.5–39.5). By comparison, only one of the 54 contacts in the 12- to 24-hour group (1.8%) was found to be carrying the same strain of the bacterium (95% confidence interval 0–5.3). This difference between the two groups was statistically significant (p < 0.001). The median age of the positive carriers (10 years) was significantly lower than the median age of the noncarriers (39 years) (p < 0.0005). This study showed that close contacts who had spent 12–24 hours with the index patient were rarely colonized with GAS. If antibiotic prophylaxis against GAS is recommended, it should probably target contacts who spent at least 24 hours with an infected patient during the week preceding illness onset. Am J Epidemiol 1999; 149:863–8.

Communicable diseases; contact tracing; disease transmission; infection; Streptococcus pyogenes

Since the late 1980s, we have witnessed a worldwide surge in the number of reported cases of invasive group A Streptococcus infection. In Sweden, the number of cases of group A Streptococcus bacteremia showed a 33 percent increase, from 1.8 per 100,000 population in 1987 to 2.4 per 100,000 in 1989 (1). In 1992, the annual incidence of invasive group A Streptococcus infection and of streptococcal toxic shock syndrome in Ontario, Canada, was 1.15 and 0.19 per 100,000 population, respectively (2).

These infections are known to be quite severe, and they have an overall 30 percent mortality rate (3). Children and elderly patients seem to be groups at higher risk for contracting these infections, as are people with certain underlying conditions such as human immunodeficiency virus infection, diabetes mellitus, and alcoholism (4). Streptococcal toxic shock syndrome, as defined by the Working Group on Severe Streptococcal Infections (5), is the most dreadful entity of all. It has been associated with a mortality rate of 81 percent (4), and until recently it was thought to afflict individuals between the ages of 20 and 50 years with no predisposing underlying diseases (3). However, in contrast to the latter finding, a large population-based study found that older patients with medical problems are more likely to develop the syndrome (4).

Many questions related to invasive group A Streptococcus infection remain unanswered—noticeably...
the risk of secondary or additional cases' occurring among close contacts of an index patient. Using the proper terminology in this setting can be challenging. Secondary cases may be additional cases being infected by a common external source, and their illness is not necessarily due to direct transmission from the initial case.

As with other serious infections such as meningococcal meningitis, chemoprophylaxis could be a solution for decreasing the risk of secondary cases. Limited evidence in the literature suggests that close contacts have a 200-fold increased risk of invasive disease (4). Data on potential target groups for antibiotic prophylaxis are almost nonexistent. If chemoprophylaxis becomes an option, it would be useful to identify the groups with an increased likelihood of infection. This study was designed to assess the relation between the prevalence of group A Streptococcus carriage and the duration of contact with a patient with invasive group A Streptococcus during the week preceding the onset of infection.

MATERIALS AND METHODS

Objectives

The aims of our study were, firstly, to quantify the numbers of contacts carrying the same strain of the bacterium as their index cases and, secondly, to make a correlation between carrier status and the intensity of exposure. The data obtained may have a significant impact in the institution of antibiotic prophylaxis for certain types of contact.

Case definition

Over a 1-year period (March 1995 to March 1996), we prospectively investigated all close contacts of patients with invasive group A Streptococcus infection, as defined by the Working Group on Severe Streptococcal Infections (5), who came to our institution (Hôpital Maisonneuve-Rosemont, Montreal, Quebec, Canada). An epidemiologic investigation was systematically performed for each index case. A questionnaire was administered to each index patient in which he or she was asked to identify all people who had spent at least 12 hours with him or her during the week preceding the beginning of the illness. Then, in order to assess the importance of exposure intensity, we divided the contacts into two groups (>24 hours of exposure and 12–24 hours of exposure). People who had spent less than 12 hours with the index patient were not included.

Throat cultures were performed in all contacts during the first 24 hours of the index patient’s hospitalization. Another throat culture was done 2 weeks later, either to confirm the eradication of group A Streptococcus in contacts who had received antibiotic prophylaxis or to increase the detection rate in the other group. A carrier was considered a positive contact if the strain found in him or her had the same serotype (proteins M and T and the presence or absence of the serum opacity factor) and the same streptococcal pyrogenic exotoxin (SPE) profile as that of the index case.

Strain analysis

The strain of group A Streptococcus isolated from an index patient or contact was first identified at our institution and was then sent to the National Centre for Streptococcus (Edmonton, Alberta, Canada) for serotyping and SPE detection by a method based on polymerase chain reaction. Serotyping was performed using standard techniques, including T agglutination reaction (6) and M typing by Ouchterlony immunodiffusion (7) or inhibition of the opacity reaction (8) for opacity factor-positive strains. Type-specific antisera used in these procedures are prepared in rabbits or guinea pigs at the National Centre for Streptococcus. Detection of the SPE genes was performed by polymerase chain reaction using a modified method based on that described by Tyler et al. (9). The different-sized amplicons generated were resolved by agarose gel electrophoresis containing ethidium bromide and were visualized under ultraviolet light.

Statistical analysis

Comparisons were made using Student’s t test for continuous variables or the chi-squared test for evaluating differences in group proportions; p values of <0.05 were considered statistically significant. Ninety-five percent confidence intervals were calculated using the formula for a proportion (10).

RESULTS

From March 1995 to March 1996, 17 cases of invasive group A Streptococcus infection were treated at our institution (table 1), and 102 contacts were screened.

Among the contacts who had spent ≥24 hours per week with the index patient, 13 out of 48 (27 percent) were found to be harboring the same serotype of group A Streptococcus as the index patient (95 percent confidence interval 14.5–39.5). By comparison, only one of 54 contacts (1.8 percent) in the second group (12–24 hours of exposure) was found to be carrying the same strain of the bacterium (95 percent confidence interval
TABLE 1. Prevalence of group A *Streptococcus* carriage among contacts of patients with invasive group A *Streptococcus* infection, Hôpital Maisonneuve-Rosemont, Montreal, Quebec, Canada, 1995–1996

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Sex and age (years) of index patient</th>
<th>Outcome of illness</th>
<th>Total no. of contacts</th>
<th>Duration of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12–24 hours/week</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No. of carriers</td>
</tr>
<tr>
<td>STSS*</td>
<td>Female, 35</td>
<td>Dead</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>STSS</td>
<td>Female, 60</td>
<td>Dead</td>
<td>2</td>
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<td>Female, 34</td>
<td>Alive</td>
<td>9</td>
<td>0</td>
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<td>Dead</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Bacteremia</td>
<td>Male, 63</td>
<td>Alive</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>Female, 40</td>
<td>Alive</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
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<td>Male, 19</td>
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<td>3</td>
<td>—†</td>
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<tr>
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<td>4</td>
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<td>4</td>
<td>0</td>
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<tr>
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</tr>
<tr>
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<td>Alive</td>
<td>3</td>
<td>—‡</td>
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<td>Male, 76</td>
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<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Total 102 1 54 13 48

* STSS, streptococcal toxic shock syndrome.
† Same as above (secondary case).
‡ None.

0–5.3). This difference was statistically significant ($p < 0.001$).

Among the 13 positive contacts, eight were children under 11 years of age, two were adolescents aged 11–20 years, and three were over 20 (figure 1). When we compared median ages between the positive carriers (10 years; mean = 16.9 years; range, 2–60 years) and the negative carriers (39 years; mean = 39.2 years; range, 1–76 years) who had spent ≥24 hours with the index patient, there was also a significant difference ($p \leq 0.0005$). The median age of the index patients was 35 years (range, 8–76 years), which was much higher than the median carrier’s age. Each index patient had, on average, 2.82 prolonged contacts (range, 1–6). Among the 17 index cases, the positive carriers were concentrated among nine cases, whereas no carriers were found among the other eight (table 1). No group A *Streptococcus* carrier was symptomatic at the time the screening was performed. When we examined the age distributions of contacts between the group with at least one positive carrier (nine index cases) and the group with no carriers (eight index cases), there was a significant difference in terms of mean age: 28.6 years versus 40.6 years ($p \leq 0.05$) (figure 2).
The first two cases listed in table 1 represent a household cluster of group A Streptococcus necrotizing pneumonia associated with streptococcal toxic shock syndrome (11). The second patient was the mother of the first patient, and they had had prolonged daily contact with one another. The cases occurred approximately 5 days apart; one child aged 9 years was a healthy carrier in the immediate environment.

All group A Streptococcus carriers were treated with a 10-day course of oral antibiotics (first or third generation cephalosporin), and control cultures performed 2 weeks later were negative.

The most commonly occurring type of protein M was the M1 type (five of 17 cases), and all of these strains carried the genetic coding for SPE A and SPE B. This is consistent with the serotype distribution observed by the National Centre for Streptococcus between April 1, 1994, and March 31, 1996, for invasive isolates and noninvasive isolates associated with serious group A Streptococcus disease (M. Lovgren, National Centre for Streptococcus, personal communication, 1997). In that collection, 26 percent of M proteins were of the M1 type, and over 96 percent of the M1 strains carried SPE A and SPE B. Overall, six contacts were found to carry beta-hemolytic streptococci which were not related to the strains of the index cases. Three patients were carrying strains of group A Streptococcus that were different from those of their index cases; two were carrying group G streptococci; and one was carrying group C streptococci. None of these contacts were symptomatic.

**DISCUSSION**

Group A Streptococcus is known to have spread from infected patients to their close contacts, but this type of transmission usually occurs in cases of pharyngitis and impetigo, and the consequences are generally benign. However, several authors have reported clusters of invasive group A Streptococcus infection (11–14), and some of them have had dramatic outcomes. In this study, the first two cases listed in table 1 represented a household cluster of necrotizing pneumonia associated with streptococcal toxic shock syndrome; in both cases, the patients died very rapidly (11). Group A Streptococcus is a frequent colonizer of asymptomatic individuals, with a carriage rate reaching 15–20 percent in children (15). In adults, the rate of asymptomatic carriage of the bacterium is known to be much lower.

Transmission of this microorganism mainly occurs through respiratory droplets, and sometimes as a result of direct contact. Fomites, on the other hand, have not been shown to be a vector of group A Streptococcus spread (15). Large studies performed in the 1950s (16, 17) showed that transmission of the bacterium between individuals is facilitated by certain factors. Acquisition of the bacterium had a direct relation with the distance between persons and the number of streptococci found in the carrier’s throat. The anatomic site of group A Streptococcus carriage also influenced transmission; transmission was higher if the bacterium was found in both the nose and the throat rather than in the throat alone. Rates of group A Streptococcus transmission are higher in individuals who have recently acquired the bacterium via the throat (16, 17).

The incidence of severe group A Streptococcus infection is on the rise. Several issues need to be addressed: firstly, the risk of invasive disease among contacts of index cases must be assessed; secondly, the potential effectiveness of antibiotic prophylaxis must be evaluated; and, finally, contacts who are at increased risk of developing a serious infection must be identified. This study dealt primarily with the latter problem.
Data on group A *Streptococcus* transmission in cases of invasive infection are scarce, and to our knowledge, few studies have clearly evaluated the prevalence of this bacterium among the contacts of patients with invasive infection. A study performed in Ontario showed that, overall, 12 percent of 152 household contacts of patients with invasive disease were harboring the same bacterial strain as the patient. No invasive illness was recorded among them (4). We found in our study that the amount of time spent with the index case during the week preceding the beginning of the case's illness was a key factor in the carriage rate. Spending at least 24 hours was associated with a significantly higher carriage rate. In the group who had spent ≥24 hours per week with the index case, carriers were significantly younger than noncarriers, and carriers seemed to be concentrated in the same household. In fact, for all index cases with a positive carrier, there was at least one child harboring the same strain of group A *Streptococcus*. By contrast, in the noncarrier group, the youngest contact was 18 years old (figure 2). This tends to support the hypothesis that children are the main reservoir for group A *Streptococcus*, and they probably transmit the bacterium to their older contacts. Most of the carriers were family members of the index patients.

Yet the risk of having an additional case can be extrapolated to be much higher among the contacts of patients with invasive infections than among the general population. The data found in this study tend to support this possibility, as do the results found by another group of investigators. Davies et al. (4) calculated that in Ontario, the estimated risk of invasive disease among household contacts was 200 times higher than in the general population. In the province of Quebec (population 7.2 million), where invasive group A *Streptococcus* infection is a notifiable disease, the rate of invasive infections was 1.4 per 100,000 population in 1995 (data from the Quebec Provincial Laboratory); one infection was a secondary case. The dramatic consequences sometimes associated with invasive group A *Streptococcus* infections raise the issue of giving antibiotic prophylaxis to contacts of these patients. In support of this practice, it is known that in cases of group A *Streptococcus* pharyngitis, patients are only contagious during the first 24 hours of adequate antibiotic treatment (18). The questions of choice of antibiotic and duration of therapy remain to be resolved. Cephalosporins seem to be adequate in terms of efficacy, and they may be superior to rifampin, which has been shown to be a rather poor choice (19). One study evaluated the duration of antibiotic prophylaxis and found that a 4-day course may be effective if using cefixime, but data for making a firm recommendation for short-term therapy are still lacking (19). In another study, clindamycin was found to be very effective among chronic group A *Streptococcus* carriers (20). One unsolved question still pertains to long-term eradication of this bacterium from carriers, who are known to be recolonized after antibiotic cessation in a good proportion of individuals.

The choice of prophylactic antibiotic and the exact duration of therapy must be carefully evaluated. The benefit of a chemoprophylaxis regimen could be determined by the number of secondary invasive cases that could be prevented. Another key question would be whether we should immediately treat all of the index patient's significant contacts or perform initial throat cultures and treat only the positive contacts. The latter approach raises the potential problem of delaying the start of antibiotic prophylaxis for at least 24 hours, and in terms of public health it could be more difficult to implement.

The results of this study pinpoint with greater accuracy the population that has a greater risk of harboring the same strain of group A *Streptococcus* as the index patient in cases of invasive infection. Studies focusing on antibiotic prophylaxis as a means of preventing secondary cases are badly needed, and such studies should probably target people who spent at least 24 hours with a patient with invasive group A *Streptococcus* during the week preceding the onset of symptoms.

**ACKNOWLEDGMENTS**

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REFERENCES