Methicillin-Resistant Staphylococcus aureus Carriage in a Child Care Center Following a Case of Disease

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Objectives: To study the prevalence of methicillin sodium-resistant and methicillin-sensitive Staphylococcus aureus colonization in a child care center following the diagnosis of community-acquired methicillin-resistant S aureus (MRSA) disease in a previously well 2½-year-old attendee and to determine the optimal site of detection of S aureus.

Design: Point prevalence survey and questionnaire administration.

Setting: A Toronto, Ontario, child care center.

Interventions: Parents were provided with general information. Consenting parents completed a questionnaire and permitted screening of their child at 1 or more sites: throat, nose, and perianal sites. Families of children who were culture positive for MRSA were offered screening and suppressive therapy. Nasal and perianal swabs were obtained from child care center staff and screened.

Results: Of 201 children, 164 (81.6%) had completed questionnaires and had undergone screening at 1 or more sites; 38 staff members (100%) completed questionnaires and were screened. A 26-month-old classroom contact with chronic dermatitis had MRSA detected only on perianal swab. Of 3 adult household contacts of the index case and 2 adult and 1 child contacts of the classroom contact, only the 7-year-old sibling of the classroom contact was positive for MRSA. By pulse-field gel electrophoresis, these isolates were identical and not related to any of the common strains circulating in regional health care institutions. Of 40 children with S aureus (24.4%), 33 had cultures at 3 sites, of which the throat was more sensitive (22 [67%]) than the nostrils (15 [46%]) or perianal sites (8 [24%]). There was a tendency for higher carriage of S aureus in children with certain risk factors, including personal hospitalization (prevalence ratio, 2.9; 95% confidence interval, 0.6-12.1), family member hospitalization (prevalence ratio, 2.0; 95% confidence interval, 0.6-6.6), and visiting the hospital emergency department (prevalence ratio, 3.2; 95% confidence interval, 0.7-14.5), all in the previous 6 months.

Conclusions: To our knowledge, this is one of the first recognized cases of MRSA disease and apparent transmission in a child care center. Throat and perianal site screenings have a higher sensitivity in identifying children colonized with S aureus than nasal culturing. Infection with MRSA should be suspected in disease unresponsive to standard antibiotic therapy.


Editor’s Note: As more and more of these infections are reported, it looks like the bugs are gaining on the drugs and guess who’s losing.

Catherine D. DeAngelis, MD

AFTER A SINGLE case of methicillin sodium-resistant Staphylococcus aureus (MRSA) infection in a child care center attendee in Toronto, Ontario, an investigation to determine the point prevalence of MRSA and methicillin-susceptible S aureus (MSSA) carriage in children and staff at the center was initiated. Another objective was to determine the prevalence of MRSA carriage among household contacts of MRSA culture-positive individuals and the optimal site of S aureus culture. A review of the English-language literature has subsequently identified 11-index case and 2 adult and 1 child contacts of the classroom contact, only the 7-year-old sibling of the classroom contact was positive for MRSA. By pulse-field gel electrophoresis, these isolates were identical and not related to any of the common strains circulating in regional health care institutions. Of 40 children with S aureus (24.4%), 33 had cultures at 3 sites, of which the throat was more sensitive (22 [67%]) than the nostrils (15 [46%]) or perianal sites (8 [24%]). There was a tendency for higher carriage of S aureus in children with certain risk factors, including personal hospitalization (prevalence ratio, 2.9; 95% confidence interval, 0.6-12.1), family member hospitalization (prevalence ratio, 2.0; 95% confidence interval, 0.6-6.6), and visiting the hospital emergency department (prevalence ratio, 3.2; 95% confidence interval, 0.7-14.5), all in the previous 6 months.

RESULTS

INDEX CASE

The index case was a 2½-year-old boy who had signs of sepsis and bilateral perforated tympanic membranes after failing to respond to macrolide therapy for otitis media. He had been attending the child care center on a full-time basis. He had a medical history of recurrent otitis media with placement of bilateral tubes at the age of 2 years. He had...
PARTICIPANTS, MATERIALS, AND METHODS

EPIDEMIOLOGICAL INVESTIGATION

All 201 children and 38 staff at the child care center were considered eligible for the study. A letter seeking informed consent and a questionnaire were distributed to all parents and staff members. Staff from the local public health department and pediatric hospital were present at the center to answer any questions from parents or staff.

The self-administered questionnaire examined sociodemographic and medical factors that may be associated with carriage of MRSA. Specifically, information about the child’s room location, age grouping, hours per week in attendance, illnesses and antibiotic use currently and in the previous month, emergency department visits, and household hospitalizations in the past 6 months was gathered.

Nasal, throat, and perianal swabs for MRSA or MSSA culture were obtained from children in June 1997, after parental informed consent was received and 2½ months after the index case was identified. Nasal and perianal swabs were obtained from child care center staff. Nasal and throat cultures were obtained from household members. All cultures were obtained at the center during a 2-day period using sterile rayon-tipped swabs and were transported directly to the Ontario Ministry of Health Central Public Health Laboratory, Toronto.

The protocol was approved by the Research Ethics Boards of The Hospital for Sick Children, Toronto, and the North York Public Health Department, North York, Ontario.

LABORATORY METHODS

All specimens received in the laboratory were planted onto blood agar and mannitol salt agar plates. After 24 hours’ aerobic incubation at 35°C, the blood agar plates were examined and possible S. aureus colonies were picked for further identification using standard methods.8 Where possible, 5 colonies suggestive of S. aureus were picked for testing. Similarly, the MRSA plates were examined at 48 hours and possible S. aureus colonies were picked for further identification. All S. aureus isolates were spotted onto Mueller-Hinton agar plates supplemented with 4% sodium chloride containing oxacillin sodium, 6 mg/L, to screen for MRSA. Susceptibility testing was performed using the agar dilution method6 on all possible MRSA isolates for the following antimicrobials: penicillin G sodium, cephalothin sodium, amoxicillin or clavulanate potassium, oxacillin, erythromycin lactobionate, tetracycline hydrochloride, chloramphenicol sodium succinate, combination of trimethoprim and sulfamethoxazole, clindamycin phosphate, vancomycin hydrochloride, and gentamicin sulfate.

All MRSA isolates were tested for the presence of the MEC gene using the polymerase chain reaction.10 The primers used were as recommended by the Molecular Typing Section of the Laboratory Center for Disease Control, Ottawa, Winnipeg, Manitoba. The genomic DNA was extracted using a commercial DNA isolation method (Puregene; Gentra Systems, Inc., Minneapolis, Minn). The extracted DNA was added to a 25-µL polymerase chain mixture containing 200 µmol/L each deoxyribonucleoside tri-phosphate; magnesium chloride, 1.5 mmol/L; Taq DNA polymerase, 1.2 U; each of the primers, 1.0 µmol/L; potassium chloride, 50 mmol/L; Tris–hydrochloric acid (pH 8.3), 10 mmol/L; and gelatin, 0.01%. The mixture was amplified for 39 cycles (94°C for 2 minutes, 55°C for 2 minutes, and 72°C for 1 minute). The polymerase chain reaction products were electrophoresed on a 1.5% agarose gel containing ethidium bromide and was photographed under UV illumination.

Molecular typing of all MRSA and methicillin-sensitive S. aureus isolates was performed using PFGE.11 Staphylococcus aureus cultures were grown overnight on blood agar plates at 37°C. The cells were harvested into a buffer consisting of sodium chloride, 75 mmol/L; and EDTA, pH 7.5, 25 mmol/L, and the turbidity, measured at 600 nm, was adjusted to an optical density of 1.5. The bacterial suspension (0.5 mL) was mixed with an equal volume of 2% low melting point agarose (SeaPlaque agarose; Mandel Scientific Co, Guelph, Ontario), pipetted into plug molds (Bio-Rad Laboratories, Mississauga, Ontario), and then allowed to solidify. For lysis, the plugs were incubated for 3 hours at 37°C with shaking, in 2 mL of lysis buffer (Tris–hydrochloric acid, 5 mmol/L; sodium chloride, 1.0 mol/L; EDTA, 100 mmol/L; 0.3% Brij 38; 0.2% sodium deoxycholate; 0.5% N-lauryl sarcosine; and lysostaphin, pH 7.5, 1 mg/mL). Following incubation, the plugs were then washed in 2 mL of washing buffer containing Tris, 10 mmol/L; and EDTA, pH 7.5, 10 mmol/L, at 55°C for 1 hour. For restriction, 2-mm slices of the agarose plugs were equilibrated at room temperature with 1× restriction buffer, as supplied by the manufacturer. After equilibration, the DNA fragments embedded in the plugs were restricted with 40 U of Smal (New England Biolabs, Mississauga) in 100 µL of 1× buffer mixture and incubated overnight at 22°C. The plugs were then loaded into 1% agarose gel (Bio-Rad Laboratories), and electrophoresis was carried out in 0.5× TBE buffer (Tris, 10.8 L; boric acid, 45 mmol/L; and EDTA, pH 8.0, 1 mmol/L) using the system (CHEF DR III; Bio-Rad Laboratories). Electrophoresis was run at 200 V with an increasing pulse time from 5 to 35 seconds for 20 hours. The gel was then stained with ethidium bromide and photographed under UV illumination.

THERAPY

Therapy with mupirocin calcium (2%) ointment to the nostrils twice daily for 5 days,12 along with daily baths with 0.3% triclosan soap,13 was provided for anyone found to be colonized with MRSA, based on reports of short-term efficacy. The addition of a combination of trimethoprim and sulfamethoxazole and rifampin, all administered orally, to this regimen was left to the discretion of the attending physician. The attainment of second cultures after therapy was recommended.

DATA MANAGEMENT AND ANALYSIS

Data were entered and analyzed using computer software (SPSS, version 6.1, SPSS Inc, Chicago, Ill). Calculation of prevalence ratios and confidence intervals of prevalence ratios was done (EpiInfo version 6.0; Centers for Disease Control and Prevention, Atlanta, Ga). Because of the low numbers in some cells, the exact method of calculating these confidence intervals is presented.
always been treated as an outpatient before this episode. At the time of presentation, MRSA was isolated in pure culture from the persisting purulent drainage in his ear canals. When the results of the culture were obtained, he was admitted to the hospital to receive intravenous vancomycin therapy. When he developed red man syndrome after the first dose, his physician changed his therapy to oral rifampin and trimethoprim-sulfamethoxazole, topical bacitracin ointment, and bacitracin and polymyxin B sulfate otic drops. He was discharged from the hospital after 7 days and completed a 14-day course of the previously described regimen as an outpatient. His family voluntarily withdrew him from the center until follow-up screening results of the nostrils, throat, and perianal areas at 1 month were negative. The results of 2 sets of follow-up cultures at 1 and 3 months were also negative.

CHILD CARE CENTER

The child care center had a total of 13 rooms for children, including an infant room and nursery. Because of the mixing of all children in the center between 7 and 7:45 AM in the playground, and through siblings in various classrooms, it was decided to include all children and staff in the study.

Of the 201 children enrolled in the center at the time of the index case’s illness, 164 children (81.6%) had completed questionnaires and had 1 or more swabs taken. Two children had withdrawn from the center at the time of the study, 14 did not return consent forms, and 19 declined participation in the study. Two children whose parents consented to the study were unable to be swabbed. All 38 staff members completed questionnaires and were swabbed.

Of the child respondents, 52% were boys and 48% were girls. Household size was 4 persons or more for 61% of the respondents, with 35% having siblings at the center; 70% of the respondents attended the center for 40 h/wk or longer. Ten percent of the respondents had someone in the household hospitalized in the previous 6 months; 7% of the children had been hospitalized in the previous 6 months; 8% were receiving antibiotics at the time of the survey; and 18% had received antibiotics in the preceding month. The mean age of children at the center was 3.2 years (range, 6 weeks to 13 years).

IDENTIFICATION OF S aureus (INCLUDING MRSA AND MSSA) BY CULTURE SITE

Forty (24.4%) of the 164 children and 9 (24%) of the 38 staff members had S aureus isolated on 1 or more swabs. Of the 164 children who were swabbed, 128 had all 3 sites swabbed, 31 had only 2 sites swabbed, and 5 had only 1 site swabbed. Further analysis of the 128 children with all 3 sites swabbed revealed that 33 were positive for S aureus on 1 or more swabs. The throat swab was the most sensitive, being positive in 22 (67%) of the 33 S aureus carriers. Nasal swabs identified 15 (46%) of the 33 S aureus carriers, and perianal swabs identified 8 (24%) of the carriers. Among these carriers, MRSA was recovered from a classroom contact, cultured at 3 sites, only on perianal swab.

MRSA IN CHILDREN AND STAFF

The MRSA-positive classroom contact was 26 months old and had a history of chronic skin disease and eczema. During the preceding 6 months, he was described by child care center staff as having hives and 2 episodes of scarlet fever. No details of his medical history could be confirmed because of the diffuse sources of his medical care. Of the 164 children in the center having 1 or more swabs, the rate of MRSA recovery (including the index case) was 1.2% (2/164). The classroom attack rate was 17% (2/12); the culture results of 2 other children who had moved to another classroom were negative; a 13th child’s parent declined screening. None of the 38 staff members were colonized with MRSA.

HOUSEHOLD CONTACTS OF MRSA-POSITIVE CHILDREN

Household contacts of the index case and the MRSA-positive classroom contact identified in the study were screened for carriage of MRSA in the throat and nostrils. None of the 3 household contacts of the index case were colonized with MRSA. Of the 3 household contacts of the classroom contact, including parents and a sibling, the 7-year-old sister was positive for MRSA on throat and nostril swab. No further history was obtained on this apparently well child.

FOLLOW-UP SCREENING OF MRSA-POSITIVE CHILDREN

Topical and systemic therapy was successful in eradicating carriage in the index case in short-term, 3-month follow-up. The classroom contact was treated with topical mupirocin and 5 days of oral trimethoprim-sulfamethoxazole and rifampin therapy, given his history of atopic dermatitis, while his family members were provided with topical therapy. At 1-month follow-up, both children were negative for MRSA at the 3 sites. Three months after the initial screening, rescreening was offered to the children and staff in the affected classroom only. Both staff members and 3 children who chose to be screened were negative for MRSA. Because of the limited transmission, we did not pursue environmental culturing.

FACTORS ASSOCIATED WITH S aureus (INCLUDING MRSA AND MSSA) CARRIAGE IN CHILDREN AND STAFF

There was a slight increase in the prevalence of carriage by age. The lowest prevalence of S aureus carriage (6%) was found in the 2-year-old group (2/32). Carriage in the first 12 months and in 1-year-olds was 33% (3/9) and 14% (3/22), respectively, while carriage in 3-, 4-, 5-, 6-, and 7-year-olds was 21% (6/28), 46% (11/24), 28% (7/25), 50% (3/6), and 44% (4/9), respectively ($\chi^2 = 7.6$ for linear trend, $P = .006$ [EpisInfo]). Other factors possibly associated with increased carriage of S aureus among children (Table), noting that the confidence intervals include 1.0 for all variables studied, include hospitalization in the past 6 months, having a family member hospitalized in the past 6 months, and visiting the emergency department at the local pediatric hospital in the past 6 months. The prevalence of S aureus carriage was not related to gender, antibiotic use at the time of the study or during the month preceding the study, classroom assignment, number of hours spent per week at the center, or the number of years attending the center.
There were 71 S. aureus isolates obtained from the center and household screening. Included in these are 3 MRSA isolates obtained from the classroom contact and his sibling. These 3 MRSA isolates and the MRSA isolate from the index case had the same susceptibility pattern: resistant to penicillin, methicillin, cephalothin, and amoxicillin or clavulanic acid and susceptible to erythromycin, tetracycline, clindamycin, trimethoprim or sulfamethoxazole, vancomycin, chloramphenicol, and gentamicin. All 71 isolates plus the MRSA isolate from the index case were further analyzed for genetic relatedness using PFGE.11 and grouped according to published criteria.11,14 All 4 MRSA isolates had banding patterns that were indistinguishable, indicating that they were all clonally related. They were not related to any of the common strains circulating in health care institutions in Toronto (F.J. and A.M., unpublished data, 1997).

The 68 MSSA isolates grouped into 12 patterns. One child was colonized by 2 unrelated MSSA strains. Thirteen children were colonized in more than 1 site by the same related strain. One pair of siblings carried the same MSSA strain. Three pairs of siblings were colonized by unrelated MSSA strains. No relationship was found between the more common isolate groups and age or classroom in the center.

## Factors Related to Staphylococcus aureus Colonization at a Toronto, Ontario, Child Care Center

<table>
<thead>
<tr>
<th>Factor</th>
<th>S. aureus Colonization*</th>
<th>Prevalence Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Having a family member hospitalized in the past 6 mo</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>34</td>
</tr>
<tr>
<td>Visiting an emergency department at the local hospital in the past 6 mo</td>
<td>Yes</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>34</td>
</tr>
<tr>
<td>Taking antibiotics at the time of survey</td>
<td>Yes</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>33</td>
</tr>
<tr>
<td>Taking antibiotics in the month before the survey</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>38</td>
</tr>
</tbody>
</table>

* Missing values were excluded. Not all participants answered all questions.

The occurrence of community-acquired MRSA in adults13,10 with minimal direct contact with health care facilities has been reported among intravenous drug users17 and aboriginal people in Australia16 and western Canada. Reports1,2,20,21 of community-acquired MRSA in children were published in the 1980s. In Chicago, Ill, the number of children hospitalized with community-acquired MRSA disease increased from 8 in 1988 to 1990 to 35 in 1993 to 1995.6,7 Methicillin-resistant S. aureus infection or colonization has been reported in 22% of the members of a high school wrestling team.22

This study represents another report of MRSA disease in a child care center attendee with minimal direct contact with health care facilities as well as apparent classroom transmission.1 Following identification in 2 Dallas, Tex, child care centers of MRSA-infected index children aged 11 and 13 months with pneumonia or empyema and, in the first center, coexisting preseptal cellulitis as well, the prevalence of colonization was 24% and 3%, respectively.1 The direction of the transmission in our center is unclear. The source of the MRSA in the classmate with dermatitis could also have been any one of a variety of his ambulatory care providers, his sister, or our index case. Dermatitis in the classroom contact actually preceded the acute ear disease in the index case by about 3 months, raising the possibility that the index case was actually a secondary case. The index case did have bilateral ear tubes placed in the hospital approximately 6 months earlier (at about the same time as the child with dermatitis was enrolled). Contact at that time with colonized personnel or environmentally contaminated objects could certainly have exposed the index case, as could subsequent contact with ambulatory care providers, but this strain is not one of those commonly circulating in health care institutions in Toronto. Strains of all 3 children have similar PFGE profiles and transmission is likely, but not confirmed.

Infants and young children have been demonstrated to remain colonized for many months, as have adults. The prevalence of colonization is surprisingly low and may reflect our 1-time prevalence survey. Transmission may also have been minimized by voluntary withdrawal of the index case until screening results at 1-month follow-up were negative. Household transmission to the 4 exposed adults did not occur, but the single sibling of the 2 MRSA-positive center attendees was MRSA-positive on throat and nostrils culture. In the family setting, colonization has been documented for 7 months or more, with at least 3 passages within the family.3 Airborne dispersal of S. aureus in nasal carriers in association with a viral upper respiratory tract infection, originally reported by Eichenwald et al23 in infants, has been demonstrated in adults.24

The throat swab provided the best yield for S. aureus in children, but perianal screening was necessary to identify the single additional MRSA-colonized child in the center. In adults, obtaining a culture from the anterior nostrils alone (with a culture of wound or sputum, when present) is an efficient method for detection of carriage.25 Adults carry 1 strain of S. aureus for highly variable periods. Prolonged carriage (>3 years) does occur, at least in the chronically ill.24 Identification of S. aureus on nonnasal sites suggests that the efficacy of topical nasal therapy alone in eradication is likely to be limited in children.

We do not know the source of MRSA in the center. The number of patients with MRSA identified in Toronto-area hospitals and nursing homes has increased rapidly from 122 patients in 1994 to 1813 in 1997. However, most patients harbor 1 of 3 PFGE types that are unrelated to the strain identified in this center. Fewer than 5% who are identified as colonized or infected with MRSA fail to have a history of having been hospitalized. In our study, possible risk factors for colonization with S. aureus (personal or household...
hospitalization or emergency department visit in the past 6 months) indicate the potential importance of hospitals to the spread of any strain of S. aureus. However, this may be more related to illness and its association with S. aureus carriage than transmission. The lack of other risk factors and the difficulty in identifying the source are well-known.

To our knowledge, MRSA has not become endemic at our hospital despite repeated introductions because of aggressive isolation of children previously hospitalized elsewhere until screening results are negative and the controlled use of suppressive therapy. We are less optimistic about the control of this organism in the child care setting than we had been before this study. There is not the same control in the real world of child care, despite extraordinary facilitation of the investigation by a highly interested and competent staff. Ultimately, the center was relieved to have only 1 child of 164 identified as positive for MRSA; at the time we had arranged the first follow-up screening, they had become fully occupied with epidemic varicella and had fewer resources to direct to this work. Also, there are limits as to how compliant busy families can be with therapy and follow-up screening, particularly when there is no clinical disease evident. Center and family factors precluded follow-up screening to measure the success of eradicative therapy.

While it is not possible to determine if failure to exclude the child with dermatitis was of importance, the recommendation that such children be excluded should be reiterated. We believe that when a child is identified with MRSA in a child care center, at a minimum, parents ought to be informed of its presence. In the event that a child becomes ill, the physician can obtain appropriate cultures earlier than usual, avoiding protracted use of ineffective antibiotics.

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