We describe the nosocomial transmission of group A Streptococcus species (GAS) from a single source patient to 24 health care workers (HCWs). DNA typing revealed that all of the isolates were identical to that of the source patient. The isolates were M type 1, positive for production of nicotine adenine dinucleotidase, and negative for opacity factor, all of which are factors reported to have a higher correlation with invasive disease. The 24 HCWs developed symptoms of pharyngitis 4 days after exposure to the source patient. Nosocomial transmission occurred 25 h after exposure to the source patient, before the institution of outbreak-control measures. A questionnaire was distributed to HCWs to help identify the factors responsible for the high attack rate among those who were exposed. Invasive GAS disease in a nosocomial setting can be highly transmissible. Rapid identification, early treatment, and adherence to infection-control practices may prevent or control outbreaks of infection.

A resurgence in cases of rheumatic fever during the mid-1980s [1, 2], followed by reports in the late 1980s and early 1990s of a new streptococcal toxic shock syndrome [3, 4] and increasing rates of streptococcal bacteremia [5], have emphasized the importance of group A Streptococcus species (GAS). Concomitantly, the seroepidemiology of GAS has changed [6–8]; M types 1, 3, and 18 are more likely to be invasive, are associated with higher case-fatality rates, and have frequently been found in clusters of infection [7–9].

Studies have indicated that nosocomially acquired GAS infection, which often occurs in clusters, accounts for 7%–14% of reported cases [10–12]. The sites of clusters of GAS infection have been divided into 3 categories: community, nursing home, and hospital [9]. The largest number of health care workers (HCWs) involved in any single cluster has been 6 [13]. We describe clonal transmission of GAS from a single patient to 24 HCWs but not to other patients.

CASE REPORT

A 43-year-old obese woman presented to the emergency department (ED) near midnight on 27 March 2001 (hospital day 1) complaining of fluid-filled blisters on her left breast. Within the next few hours, the lesions coalesced, spread, were accompanied by burning pain, and began to slough. She experienced emesis and watery diarrhea.

She reported a 3-day history of upper respiratory symptoms and fever. She denied drug allergies, recent
bites, chemical exposures, travel, and use of intrauterine devices, tampons, tobacco, alcohol, or illicit drugs. Her family history was remarkable for diabetes.

Examination of the patient revealed the following values: temperature, 36°C; blood pressure, 128/68 mm Hg; pulse, 128 beats/min; respiratory rate, 30 breaths/min (oxygen saturation of 90% in room air); and weight, 186 kg. She had moderate respiratory distress. Notable findings included obesity, minimal posterior pharyngeal injection, and an irregularly irregular heart rhythm.

There was a single, demarcated 20 × 40 cm patch of hemorrhagic denuded skin on the left breast; Nikolsky sign was present. Sensation was intact to pinprick. No breast masses, fluctuance, or nipple discharges were noted. Values noted during laboratory studies were within normal ranges, with the following exceptions: WBC count, 11.8 × 10^9 cells/L (high); hemoglobin, 10.8 g/dL (low); hematocrit, 34.6% (low); chloride, 97 mM (low); HCO₃, 12 mM (low); blood urea nitrogen, 26 mg/dL (high); creatinine, 4.7 mg/dL (high); ionized calcium, 0.95 mg/dL (low); phosphorus, 7.7 mg/dL (high); magnesium, 1.3 mg/dL (low); aspartate aminotransferase, 131 U/L (high); total bilirubin, 3.5 mg/dL (high); and direct bilirubin, 2.4 mg/dL (high). Levels of salicylates and acetaminophen in blood were within normal limits. Gram staining of respiratory secretions obtained through a nasotracheal tube revealed 5–30 cells of unknown type per high-powered field and no organisms; rare GAS was recovered from culture. No throat samples were obtained for culture. The electrocardiogram revealed atrial fibrillation. Chest radiography revealed pulmonary edema and a retrocardiac opacification.

The patient received intravenous vancomycin, clindamycin, and piperacillin-tazobactam for treatment of probable streptococcal or staphylococcal infection, and she was admitted to the intensive care unit (ICU). Endotracheal intubation was attempted without success. Nasotracheal intubation was performed successfully. A skin biopsy was performed. Hemodialysis was initiated for treatment of acute renal failure. The findings of a pelvic examination were unremarkable.

On hospital day 2, a bedside ultrasound examination of the breast ruled out occult abscesses. The skin biopsy demonstrated necrotizing dermatitis and gram-positive cocci. On the hospital day 4, penicillin-, clindamycin-, and erythromycin-susceptible isolates of GAS were recovered from blood cultures, respiratory secretions, and the breast lesion.

Intravenous immunoglobulin was given twice, with transient improvement in the hemodynamics each time. On hospital day 6, a bedside mastectomy was performed. Necrosis extended from the skin to the deep edge of the resection. Organisms were visualized, and cultures confirmed the presence of abscesses throughout the breast tissue. *Escherichia coli* and *Klebsiella pneumoniae* were isolated from cultures of blood samples obtained on the tenth hospital day. The patient died on the seventeenth hospital day. Autopsy confirmed small-bowel ischemia with perforations.

**MATERIALS AND METHODS**

**Investigation of the outbreak and interventions.** On the morning of the fourth hospital day, 3 ICU nurses who had cared for the patient during the prior 24–60 h reported that they were ill with similar symptoms of fever, sore throat, and general malaise. Until that time, the patient had been treated with “standard precautions” [14]. During hospital day 4, “special organism precautions” (contact precautions [14]) were instituted. By the end of the fourth hospital day, an additional 16 symptomatic HCWs were identified who had been in contact with the patient.

**Surveillance definition.** Our surveillance case definition included symptomatic HCWs with direct patient contact (defined as touching the patient or the bed) or who had been face-to-face with the patient within 3 feet. Subjects with “symptomatic” cases were those who met ≥1 of the following criteria: documented or perceived fever, sore throat, new unexplained myalgia or arthralgia, and malaise. Symptomatic individuals were evaluated, had throat samples obtained for culture, and received antibiotic treatment. They were excused from work and allowed to return after 24 h of therapy and improvement. Nineteen individuals met this initial case subject definition.

**Therapy.** Different antibiotic regimens were prescribed, as follows: penicillin V, 1000 mg b.i.d. for 10 days (received by 1 HCW); penicillin V, 500 mg q.i.d. for 10 days (received by 15 HCWs, including the self-treated resident physician); penicillin V, 250 mg q.i.d. for 10 days (received by 4 HCWs); azithromycin, 500 mg q.i.d. for 10 days (received by 1 HCW, who self-reported receipt of concurrent treatment with penicillin); and azithromycin, 500 mg q.i.d. for 5 days (received by 1 HCW). One additional HCW began a course of azithromycin that was discontinued after 1 dose because of an adverse reaction; the treatment was changed to orally administered clindamycin, 300 mg every 6 h for 7 days. One HCW declined follow-up, and his outcome is unknown. Asymptomatic HCWs with positive culture results were advised to complete a 10-day...
course of antibiotic treatment; asymptomatic HCWs with negative culture results were advised to discontinue treatment.

**Throat cultures.** Throat cultures were processed and grouped in the Clinical Microbiology Laboratory at the University of California San Francisco Medical Center. Serogrouping was confirmed at the World Health Organization (WHO) Collaborating Center for Reference and Research on Streptococci at the University of Minnesota (Minneapolis).

**DNA typing.** The GAS isolated from the patient (4 isolates), the HCWs (24 isolates), and the son of one HCW (1 isolate) were typed by the Molecular Epidemiology Laboratory at Stanford University (Stanford, California).

**Preparation of chromosomal DNA.** After preparation of the chromosomal DNA, PFGE was performed using the Bio-Rad Chef II system and their preset enterococci program for 20 h at 14°C. Gels were stained with ethidium bromide and photographed (figure 1).

**M typing, opacity factor (OF) determination, and nicotine adenine dinucleotide (NADase) production.** GAS isolates were characterized at the WHO Collaborating Center for Reference and Research on Streptococci at the University of Minnesota. M typing and T agglutination pattern identification were performed using standard methods [15]. M typing precipitin reactions were performed with use of the Ouchterlony double-diffusion method of Rotta et al. [16]. Detection of streptococcal serum OF and OF serotyping were done by use of techniques described by some of us (E.L.K. and D.R.J.) elsewhere [17]. Levels of NADase, an extracellular enzyme that is highly correlated with invasive strains of GAS, were also measured in all 29 strains using qualitative and quantitative assays [18].

**Questionnaire.** A questionnaire, with an option for anonymous completion, was developed and distributed to 141 exposed HCWs during the week of 7 May 2001. These 141 HCWs were identified as having been exposed to the source patient or having provided a throat sample for GAS culture. Contact with the patient was defined as ≥1 of the following: (1) being face-to-face within 3 feet but without touching the patient, (2) touching the patient or her environment, or (3) touching the patient’s respiratory secretions, ventilator equipment, or attached tubing. Questionnaires were completed as early as 17 April 2001 and as late as 8 July 2001; the majority (55 of 67) were completed during the month of May.

**Statistical analysis.** A person with a confirmed nosocomial case was defined as an HCW who was symptomatic and culture positive (n = 23). We included as a case subject a resident physician who had repeated contact with the patient, developed symptoms that met the surveillance case definition, and was self-treated without a throat culture (N = 24). A retrospective case-control analysis was performed to identify factors that may have increased the risk of transmission to HCWs. Seventeen case HCWs and 50 control HCWs who returned the questionnaire were compared. EpilInfo 2000 software was used to perform the frequency and contingency analyses and to compute the descriptive statistics. P < .05 was considered to be statistically significant.

**RESULTS**

**Throat cultures and DNA typing.** From 30 March through 13 April 2001, a total of 143 throat samples were obtained for culture related to this cluster (132 from HCWs, 5 from patients neighboring the patient, and 6 from family members of HCWs and patients, including the source patient’s mother). Nine HCWs whose names appeared on the exposure list did not provide samples for culture for unknown reasons. Of the 132 HCWs, 80 (61%) reported having ≥1 of the symptoms included in the surveillance definition. Twenty-four (18%) of 132 cultures of throat samples obtained from HCWs were positive for GAS. Twenty-three (96%) of 24 isolates had a DNA pattern that was identical to that of the patient’s isolate. The lone HCW whose pattern was different had 2 symptomatic children; the throat culture for 1 of the children was positive and had a DNA pattern that was identical to that for the mother. Because this individual’s strain was not the clonal strain, it was excluded.
from analysis. No cases of transmission to patients or family members were identified.

**M typing, OF, and NADase production.** Twenty-seven of 29 strains (1 each recovered from 23 HCWs and 4 recovered from the patient) of GAS were M type 1; the 2 discordant strains (1 recovered from an unexposed nurse and 1 recovered from her son) were M type 12. All produced NADase and were OF negative. The mean quantity of NADase produced was 2.92 for M type 1 strains and 2.63 for M type 12 strains [18].

**Outcome of therapy.** For follow-up cultures, throat samples were obtained from 22 (92%) of 24 HCWs whose initial cultures were positive, as well as those HCWs who remained symptomatic after treatment, regardless of the initial culture result. Two individuals had positive results of follow-up cultures; in both, the initial cultures had been positive. Both individuals had received penicillin V, 500 mg q.i.d. for 10 days, and both were re-treated with a second identical course, after which their culture results were negative. Three HCWs whose initial culture results were positive received a second course of therapy for persistent symptoms, although their follow-up cultures were negative. Two of the 3 were initially treated with penicillin V, 250 mg q.i.d. for 10 days, and 1 was treated with penicillin V, 500 mg q.i.d. for 10 days. All 3 were re-treated with penicillin V, 500 mg q.i.d. for 10 days. One additional HCW received a second course of therapy (clindamycin, 300 mg every 6 h for 7 days) when her clinician was erroneously informed that her follow-up culture result was positive (table 1).

**Demographic characteristics and exposure analysis of HCWs.** Sixty-seven (47.5%) of 141 HCWs on the list of exposed persons returned the questionnaire. An analysis of job titles indicated that those who returned the questionnaire were representative of the whole group.

Seventeen (71%) of 24 HCWs who were considered nosocomial cases returned the questionnaires and were used as cases for the case-control analysis; 16 were culture positive, and 1 was the self-treated resident. Fifty (43%) of 117 HCWs who were not considered to have cases returned questionnaires (P < .05) and were considered to be control subjects. Of the 67 respondents, 44 (65.7%) were female, 22 (32.8%) were male, and 1 (1.5%) declined to answer the question. The age range was 22–64 years, with a mean age (±SD) of 37 ± 10 years. Of those persons considered case subjects, 9 were female and 8 were male. The age range for this group was 26–48 years, with a mean age (±SD) of 34 ± 7 years. Case subjects included 7 nurses, 8 doctors/residents (including an anesthesiologist), and 2 radiology technicians.

Fifty-four (80.6%) of 67 respondents reported having had contact with the index patient, and 13 (19.4%) reported having had no contact. Of the 54 individuals who reported contact, 2 had contact in the ICU and the ED, 5 had contact in the ED only, and 47 had contact in the ICU only. Both persons who had contact with the patient in the ED and the ICU reported touching the patient’s respiratory equipment or secretions as well as the patient and/or her environment; both were case subjects. Of the 5 whose contact occurred only in the ED, 1 was a case subject who reported touching the patient’s respiratory equipment or secretions. Of the other 4 HCWs who had contact in the ED, 3 reported contact with the patient and/or her environment, 2 reported contact with the patient’s respiratory equipment or secretions, and 2 were face-to-face with the patient without physical contact. Of the remaining 47 HCWs who had contact in the ICU, 44 reported contact with the patient and/or her environment, 29 reported contact with the patient’s respiratory equipment or secretions, and 18 were face-to-face with the patient without physical contact.

Thus, a total of 16 (29.6%) of 54 HCWs who reported contact with the index patient were infected and 38 (70.4%) of 54 were not. No statistically significant correlation between the location of contact or type of contact and becoming a case subject or developing symptoms was observed when all dates were considered.

Although several people had multiple exposure dates, what appeared to be most significant was earlier initial exposure (figure 2). When each date of contact was considered independently, there was a statistically significant correlation (P < .05) between contact on day 2 and becoming a case subject. This held true only when contact was defined as touching the patient or the patient’s secretions, but not when the HCW did not have such physical contact.

Of the 13 (19.4%) of 67 respondents who reported no contact with the source patient, 2 had positive culture results; one respondent had a community-acquired case, and the other reported that she entered the patient’s room on day 2 of hospitalization but did not have contact with the patient. All 13

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Table 1. Summary of transmission of group A *Streptococcus* and treatment of infections in health care workers (HCWs).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
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</thead>
<tbody>
<tr>
<td>Questionnaires distributed</td>
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</tr>
<tr>
<td>Questionnaires returned</td>
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</tr>
<tr>
<td>Confirmed nosocomial cases in HCWs</td>
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<tr>
<td>Transmission to patients</td>
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</tr>
<tr>
<td>Transmission to family members of HCWs</td>
<td>0b</td>
</tr>
<tr>
<td>Nosocomial cases treated with penicillin</td>
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</tr>
<tr>
<td>Microbiological failures that required re-treatment</td>
<td>2</td>
</tr>
<tr>
<td>Clinical failures that required re-treatment</td>
<td>3</td>
</tr>
<tr>
<td>Nosocomial cases treated with other antibiotics</td>
<td>3</td>
</tr>
<tr>
<td>Failures that required re-treatment</td>
<td>0</td>
</tr>
</tbody>
</table>

*a* Five samples were obtained from neighboring patients for culture; all results were negative.

*b* Per follow-up by the San Francisco Department of Public Health.

*c* Defined as a positive throat culture after the completion of therapy.

*d* Defined as the persistence of symptoms for the duration of therapy.
of these HCWs, however, reported that they had developed ≥1 symptom defined in the questionnaire. Of the 11 HCWs who reported no contact with the source patient and whose throat culture results were negative, 8 (73%) reported contact with a symptomatic HCW who had contact with the patient (i.e., secondary contact).

Respondents were requested to answer with “always,” “sometimes,” or “never” with regard to the use of personal protective equipment (table 2). For the analysis, “sometimes” and “never” were both considered to represent noncompliance, and a response of “always” was considered to represent compliance. If any personal protective equipment choice had been marked with any response, “never” was assumed for any remaining unanswered choices. No significant protective effect was demonstrated for use of any type of personal protective equipment.

Fifteen (94%) of 16 HCW case subjects who responded to the questionnaire reported using soap and water to wash their hands after contact with the source patient; 1 HCW case subject reported using alcohol gel. Of the HCWs with contact who were not case subjects and who answered the questionnaire, 36 (95%) of 38 also reported soap and water use (P > .05).

DISCUSSION

GAS infection can be readily transmitted to HCWs [13, 19]. In the outbreak of infection we report, 24 HCWs developed symptomatic pharyngitis ≤4 days after coming into contact with a patient who had invasive GAS infection. The attack rate in this clonal outbreak is high regardless of whether it is calculated using the cohort of all HCWs who received the questionnaire (24 [17%] of 141) or only the HCWs who returned the questionnaire (17 [25%] of 67). We propose that this high rate of transmission was due to the presence of GAS cutaneous infection and bronchopneumonia in the patient.

On the basis of its M type, NADase production, and severity of illness in the patient, this GAS infection was determined to be invasive, yet all 24 symptomatic HCWs developed only pharyngitis. This suggests, but does not prove, that the early identification and treatment of contacts may have prevented the development of invasive disease. The isolates in this cluster were M type 1 and were positive for the production of NADase [18]. Strains with these features are more likely to be invasive, to have higher case-fatality rates, and are associated with clusters of infection [7]. Our observations are consistent with those in reports published elsewhere that have described the seroepidemiology of GAS infection [6–8].

Thirty of 67 HCWs who returned the questionnaire reported that they had ≥1 of the symptoms included in the case definition; the throat culture was negative for these 30 HCWs. The rate of false-negative results for GAS throat culture in symptomatic individuals is estimated to be ~10% [20]. Thus, we may have failed to identify ~3 additional positive culture results among these 30 HCWs.

Transmission to patients was not observed, although active
surveillance was not conducted. Five negative culture results were noted for neighboring patients, and no cases were identified by physicians who had been alerted. Transmission occurred among HCWs who had contact with the index patient ≥25 h after the patient’s admission to the hospital, before the institution of the outbreak-control measures, which included contact precautions for the patient, work restriction, education, and rapid identification and treatment of contacts. We propose, but cannot prove, that the latter may have prevented GAS transmission to other patients.

We were unable to demonstrate that the use of particular personal protective equipment was related to transmission. The patient underwent intubation, extubation, and reintubation on day 2 of hospitalization; it is likely that aerosolization of infected respiratory secretions occurred at this time. This may explain why the patient’s mother was culture negative, despite having had unprotected contact before admission. The effectiveness of contact precautions on the fourth day cannot be ascertained from these data; the transmissibility of the patient’s infection starting on day 3 of hospitalization may have been reduced by the intravenously administered antibiotic therapy.

Because reported compliance with hand washing measures was high in the case (94%) and control (95%) groups, we were unable to demonstrate that hand washing practices were related to the risk of infection. There was transmission of the clonal strain to a nurse who reported entering the patient’s room but who did not have contact as defined above. This individual stated that she did not wash her hands when she left the room and may have acquired the organism through contact with a contaminated inanimate object or with an unidentified, infected coworker. Contamination of inanimate objects may have contributed to an outbreak of GAS infection in a child care center that was reported elsewhere [21]. The role of such contact in this outbreak has not been defined. The decision to return the questionnaire may have been biased by a reluctance to report noncompliance. Bias may also have been introduced by the prolonged time interval (~2 months) between the event and the submission of the questionnaire.

One suggested strategy for the treatment of symptomatic or asymptomatic HCWs who have pharyngeal colonization with GAS is oral administration of penicillin, 500 mg q.i.d. for 10 days, with orally administered rifampin, 600 mg q.d. for the last 2 days of therapy [22, 23]. Rifampin was not used in this cluster. Of the 19 HCWs who received penicillin and who had a throat culture positive for GAS, 17 (89%) were culture negative on the first follow-up visit. The resident physician also received penicillin, and his symptoms resolved after a single course of therapy. Symptoms resolved in 17 (85%) of 20 HCWs treated with penicillin; 3 persistently symptomatic HCWs were re-treated with penicillin V, even though the follow-up throat culture for each was negative. Rheumatic fever, carditis, and nephritis were not noted. These data indicate that use of penicillin V alone was effective and safe for management of these GAS infections.

The infection-control policy for adult and pediatric patients in effect at our institution at the time of the outbreak required that only standard precautions be used for respiratory (e.g., pharyngitis or pneumonia) or wound infections with GAS. Transmission-based (droplet or contact) precautions were not required. This policy for adults was consistent with the 1996 Guideline for Isolation Precautions in Hospitals [14]. Although this organism had characteristics that have been associated with clusters and invasiveness, we are uncertain as to the reasons for its extensive transmission to HCWs. Thus, changes to the policies for both adult and pediatric patients were implemented after this outbreak of infection. Droplet precautions are now required for patients with suspected or confirmed GAS respiratory infections, such as pharyngitis or pneumonia. Contact precautions are required for patients with suspected or confirmed wound or necrotizing skin infections due to GAS. The latter patients are also assessed for potential

<table>
<thead>
<tr>
<th>Equipment</th>
<th>No. of case subjects (n = 16)</th>
<th>No. of control subjects (n = 38)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compliant with use</td>
<td>Noncompliant with use</td>
<td>Compliant with use</td>
</tr>
<tr>
<td>Gloves</td>
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<td>3</td>
<td>31</td>
</tr>
<tr>
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<td>Goggles</td>
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</tr>
<tr>
<td>Prescription glasses</td>
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</tr>
<tr>
<td>Full face shield</td>
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<td>2</td>
</tr>
</tbody>
</table>

NOTE. NA, not applicable.

Table 2. Use of personal protective equipment by 54 health care workers who reported contact with the index patient.
respiratory infection due to GAS, and droplet precautions are added if infection is suspected or confirmed.

References