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Outbreak Due to Methicillin- and Rifampin-Resistant *Staphylococcus aureus:* Epidemiology and Eradication of the Resistant Strain from the Hospital

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ABSTRACT

A methicillin- and rifampin-resistant strain of *Staphylococcus aureus* was introduced into a university hospital by interstate transfer of an infected surgical patient. An outbreak occurred, and 17 patients became infected or colonized with the epidemic strain. Reservoirs appeared to be patients who were infected or colonized with the resistant *S aureus* and possibly two nurses who were nasal carriers. The outbreak isolate was likely spread by contact with contaminated hands of personnel. A retrospective case-control study identified tracheostomy, débridement, and irrigation of wounds by power spray and prolonged nasogastric intubation as risk factors for acquisition of the epidemic strain. Analysis of factors by groups indicated that surgical procedures, wound care procedures and instrumentation of the respiratory tract were significantly associated with cases. The nasal carrier state was eradicated in two nurses by topical application of 5% vancomycin. The epidemic strain was eradicated from the hospital 8 months after it was introduced. [Infect Control 1987; 8(1):15-23.]

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INTRODUCTION

Methicillin was introduced in England in 1959. Within a short time of its introduction, the first methicillin-resistant *Staphylococcus aureus* (MRSA) strains were reported by Jevons.[1] The first large outbreak in the United States occurred at Boston City Hospital in 1968.[2] Over the past 10 years, there have been increasing numbers of reports of outbreaks caused by MRSA from tertiary care medical centers.[3-16] In published reports the severely debilitated patient seems to have been at greatest risk for acquiring this organism. Most cases have occurred in surgical patients[5,6,12-15] and burn patients.[4-6,9,14]

In July 1981, MRSA was introduced into a university hospital by the interstate transfer of an infected surgical patient. Unlike previous reports of MRSA, this organism was also resistant to rifampin (minimal inhibitory concentration >5 μg/ml). Over the next 8 months, a total of 17 patients and three personnel became colonized or infected with the methicillin- and rifampin-resistant *S aureus* (MRRSA). An epidemiologic investigation was carried out, and the epidemic strain was eradicated from the patient population after effective epidemiological control measures were instituted.

The purpose of this communication is to describe the epidemiological aspects of the MRRSA outbreak and the unique control measures that led to the organism's eradication from our hospital.

MATERIALS AND METHODS

Epidemiological Methods

Laboratory records were reviewed for 6 months prior to the outbreak for cultures positive for MRRSA.

A case of colonization was defined as any patient with a culture positive for MRRSA, from any site, without evi-

dence of tissue invasion. Infection with MRRSA was defined as evidence of invasive disease accompanied by a pure culture of MRRSA from the site of involvement. The following case definitions were applied: 1) bacteremia: one or more blood cultures positive for MRRSA; 2) urinary tract infection: a urine culture with $\geq 10^5$ colony forming units (cfu) per ml of MRRSA from either a clean voided specimen or a specimen aspirated from an indwelling catheter; 3) pneumonia: culture of respiratory secretions positive for MRRSA and a new pulmonary infiltrate on chest roentgenogram; 4) pleural empyema: presence of purulent fluid in the pleural space culture-positive for MRRSA; 5) catheter site infection: purulent drainage from a catheter site that was culture-positive for MRRSA or ≥ 15 cfu of MRRSA on semiquantitative culture by the technique of Maki and associates[17]; 6) wound infection: purulent drainage from a wound that was culture-positive for MRRSA; 7) osteomyelitis: a bone biopsy culture-positive for MRRSA; and 8) intra-abdominal abscess: abscess in the abdominal cavity from which purulent fluid taken at surgery yielded MRRSA on culture.

A retrospective case-control study was performed. Two controls were selected for each case. The following criteria were used to identify appropriate controls: 1) exposure to MRRSA for at least 48 hours on a nursing unit where a MRRSA case was hospitalized; 2) two or more sets of negative cultures for MRRSA from the patient on two or more different days. The average number of sets of cultures for controls was 5.7 with a median of 3 and a range of 2 to 24. Twenty-eight of 34 controls (82%) were hospitalized on the same nursing units as the cases for which they were selected. Twenty of the 34 controls (59%) were hospitalized on the same nursing unit at the same time as the cases for which they were chosen. Since the outbreak was small and well defined, it was clear that some cases and controls were housed for part of their hospitalization in areas of the hospital where they had no contact with patients culture-positive for MRRSA. For this reason, data on potential risk factors were collected for cases and controls only during the periods when they were at risk, because they were hospitalized on a unit where a patient culture-positive for MRRSA was present. Exact periods of exposure could be determined for each of the controls. For five patients who became cases, no exposure to a case could be documented. The period of exposure for four of these cases was defined as the time from admission until first positive culture for MRRSA. The period of exposure for the remaining case was the period from the time of her admission to the General Surgery Intensive Care Unit until her first positive culture for MRRSA. MRRSA were acquired by 14 case patients in an intensive care unit, by one case patient on a general surgical nursing unit and by one case patient on a general medical nursing unit. The source of MRRSA for the remaining case was unknown. Thirty-two controls were selected from intensive care units and two from a general medical nursing unit. The same data were recorded for cases and controls. Information extracted from patient charts included demographic data, admission date, primary and secondary diagnoses, hospital service and location, instrumentation, procedures, operations, antibiotics, and culture results with antibiograms. The primary diagnosis(es) was the admitting diagnosis(es), and the secondary diagnoses were associated or underlying diseases.

Culture Sampling Methods

Surveillance cultures and contact tracing cultures were taken from patients' anterior nares, skin lesions (including surgical wounds and decubiti) and sputum. Cultures of anterior nares and skin lesions were taken with sterile cotton swabs and sputum specimens were obtained with sterile suction catheters and Luken's traps. Contact tracing cultures were taken from each contact weekly until discharge or until the patient had four negative sets of cultures.

Cultures were taken from hospital personnel from anterior nares and hands using sterile cotton swabs. For hand cultures, cotton swabs were premoistened with sterile saline. At the time of culture, the hands and forearms of personnel were examined for evidence of infection and dermatitis.

Cultures were taken from environmental surfaces using sterile cotton swabs premoistened with sterile saline.

Studies for possible airborne transmission were performed in the intensive care unit where some of the MRRSA patients were cohorted using a Microban Air Sampler (Ross Industries, Midland, VA) and an Anderson 2-stage air sampler (Anderson Sampler, Inc., Atlanta, GA). The air samplers were placed at a height of 18 inches, and baseline samples were taken at distances of 4, 12, and 28 feet from each patient (Figure 1). Following various types of manipulations that might be expected to produce aerosolization of MRRSA, cultures were again taken at four and twelve feet from each patient. For one patient, samples were taken during and after vigorously flapping the sheets five times. For a second patient, cultures were taken after a dressing change. Samples were taken after a third patient had a dressing change and power spray treatment of the wound. During power spray, a fine mist of hydrogen peroxide and saline is blown into the wound under pressure for débridement. For a fourth patient with sputum cultures positive for MRRSA, samples were taken after endotracheal suctioning which stimulated vigorous coughing.

Microbiological Methods

Clinical specimens were processed in the hospital laboratory. Surveillance cultures from patients and cultures from personnel and environment were processed in the Hospital Epidemiology Laboratory using a selective medium. For the first cluster of cases, the selective medium consisted of 5% sheep blood agar with 5 μg/ml of gentamicin. After the patients of the first cluster were identified, staphylococcus 110 agar containing 20 μg/ml of methicillin was used as the selective medium. Cultures of air were performed using mannitol salt agar containing 20 μg/ml of methicillin. All plates were stored at 4°C and used within 2 weeks of their preparation. Controls for each set of cultures included one plate inoculated with an isolate of MRRSA and one plate inoculated with a methicillin-sensitive strain of *S aureus*. Cultures were incubated at 37°C until positive or for 72 hours. Isolates were identi-

fied as *S aureus* by macroscopic and microscopic morphology and by a positive tube coagulase test. Isolates of *S aureus* were identified as methicillin-resistant by growth on media containing 20 μg/ml of methicillin. Isolates of *S aureus* resistant to methicillin were identified as MRRSA when they grew on media containing 5 μg/ml of rifampin. Methicillin resistance was confirmed by inoculating 10^8 cfu from an overnight broth culture onto Mueller-Hinton Agar containing 20 μg/ml of methicillin.

Broth dilution susceptibility tests were performed by a technique published previously.[18] The inoculum was 5×10^5 cfu/ml. All susceptibility tests were carried out in microtiter plates in a final volume of 0.1 ml per well. The minimal inhibitory concentration was defined as the lowest concentration of drug which suppressed visible growth after incubation at 35°C for 18 hours. The minimal bactericidal concentration was determined by transferring 0.01 ml from the microtiter wells to sheep blood agar plates and incubating at 35°C for 18 hours. The minimal bactericidal concentration was defined as the lowest concentration of drug which yielded fewer than two to three colonies (99.9% kill) on subculture.

Statistical Methods

Data were punched onto computer cards and analyzed using the SAS statistical package (SAS Institute, Inc., Cary, NC, 1982) and university computer resources. The statistical tests used for univariate analysis included the chi-square test, Fisher's exact test, and the *t*-test. Logistic regression analysis was performed using a procedure from the SAS Supplemental Library User's Guide.

RESULTS

Description of the Outbreak

The Medical College of Virginia Hospitals constitute a 1000-bed tertiary care center. There are eight intensive care units and a burn center. The outbreak began on July 17, 1981 when the index case was transferred from a Florida hospital to our institution and was admitted to the General Surgery Intensive Care Unit for treatment of vascular graft infections due to MRRSA. Hospital personnel were unaware that the patient was infected with MRRSA, and he was not placed on isolation. The presence of the MRKSA infection was first noted by the Hospital Epidemiologist who was asked to see the patient for an Infectious Disease consultation. The patient was immediately placed on isolation, and a point prevalence culture survey was done using a selective medium for MRRSA. All patients in the General Surgery Intensive Care Unit were culture-negative for MRRSA. The first secondary case was identified 4 weeks later at which point control measures were put into effect (Figure 2). Cultures of contacts of the index case and first secondary case yielded three additional cases. These patients were placed on strict isolation, and their contacts were cultured until they had four negative sets of cultures or were discharged. No further cases occurred for 10 weeks. Then, a new case was discovered when the Hospital Epidemiology Unit was notified by the hospital laboratory about a MRRSA isolate from a patient in the General Surgery Intensive Care Unit. The patient was isolated, and all contacts were cultured weekly until they were discharged. Control measures were intensified

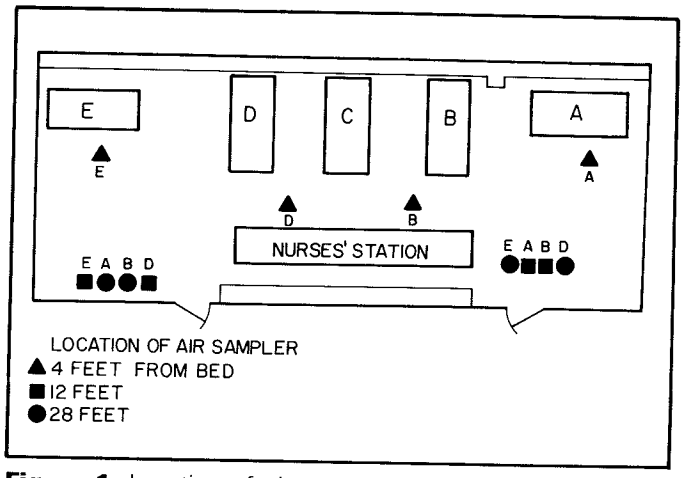

Figure 1. Location of air samplers during study of airborne transmission. Patients were located in beds A, B, D, and E.

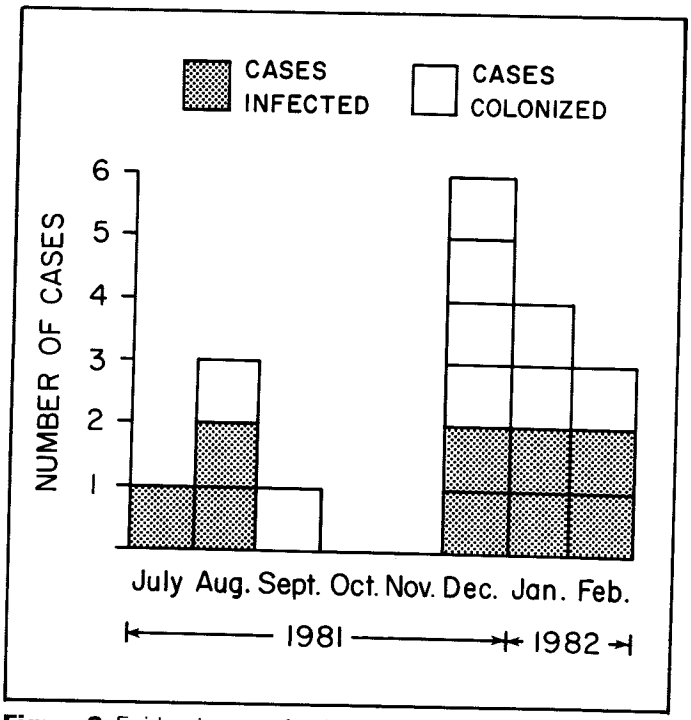

Figure 2. Epidemic curve for the outbreak caused by methicillin- and rifampin-resistant *Staphylococcus aureus*.

by placing all patients transferred from the General Surgery Intensive Care Unit in strict isolation until four negative sets of cultures were obtained. The second cluster occurred in a large geographic area. Surveillance cultures and cultures of contacts were done on surgical units and in intensive care units where cases had been hospitalized. These cultures identified 6 more patients who were positive for MRRSA.

In the first week of 1982, the decision was made to cohort MRRSA patients into one area. Since two MRRSA patients required intensive care, it was decided to establish the cohort in a five-bed surgical intensive care unit. From the time of the establishment of the cohort until the time the outbreak was controlled, three more cases were discovered by culture of contacts and surveillance cultures,

TABLE 1
ANALYSIS OF DEMOGRAPHIC CHARACTERISTICS AND DIAGNOSES AS RISK FACTORS FOR ACQUISITION OF MRRSA

Factor	Controls (n = 34)	Cases (n = 17)	*P*-Value
Sex			0.67*
Males	24	11	
Females	10	6	
Race			0.68*
Black	15	9	
White	18	8	
Other	1	0	
Age in years mean (SD)	55.0 (19.3)	50.3 (21.5)	0.44†
Time hospitalized prior to exposure in days, mean (SD)	12.0 (20.4)	8.7 (11.8)	0.47‡
Length of exposure in days, mean (SD)	14.1 (16.7)	14.8 (10.7)	0.88†
Number of diagnoses			
Primary mean (SD)	2.4 (1.3)	2.8 (1.4)	0.28†
Secondary mean (SD)	1.8 (1.6)	2.9 (1.6)	0.023†
Combined mean (SD)	4.2 (2.2)	5.8 (2.0)	0.017†

**chi-square test*
†t-test
‡t-test (approximate for unequal variances)

TABLE 2
ANALYSIS OF PROCEDURES AS RISK FACTORS FOR ACQUISITION OF MRRSA

Factor	Controls (n = 34) Mean (SD)	Cases (n = 17) Mean (SD)	*P*-Value
Power spray	1.47 (3.0)	5.47 (6.5)	0.026*
Endotracheal suctioning	15.08 (20.8)	28.24 (25.2)	0.053†
Wound irrigation	0.0 (−)	1.17 (2.7)	0.09*
Dressing changes	6.35 (10.0)	9.76 (9.7)	0.25†
Endoscopy	0.18 (0.5)	0.00 (−)	0.17*
Foley catheter irrigation	0.26 (1.1)	0.06 (0.2)	0.29*
Drain irrigation	1.79 (10.3)	3.35 (6.9)	0.52†
Straight catheterization	0.38 (2.2)	0.17 (0.8)	0.63*

**t-test (approximate for unequal variances)*
†t-test

and one case was discovered by recovery of MRRSA from a clinical specimen. The last two cases occurred on February 22 and 23, 1982. There were no cases in the burn center. The attack rate was 17 cases in 415 patients at risk (exposed to a case for any length of time) or 4.1%. Review of hospital laboratory records for the six months before the outbreak revealed no isolates of MRSA or MRRSA. In the 4½ years since termination of the outbreak, 255 isolates of MRSA have been tested for susceptibility to rifampin. Only two isolates were resistant to rifampin; one was detected in July 1984 and one in July 1985. Plasmid patterns have been determined for 52 of the 255 isolates, and all patterns were different from that of the epidemic strain.

Description of Cases

Of 17 cases, eight patients were infected and nine patients were colonized with MRRSA. Types of infection included bacteremia, postoperative wound infections, osteomyelitis, intravenous catheter wound infection, intra-abdominal abscess, pleural empyema, and urinary tract infection. Infected patients had from one to three sites of infection.

Sites culture-positive for MRRSA in the nine colonized patients included anterior nares, postoperative wounds, decubiti, respiratory tract, eyes, and an intravenous catheter site. Colonized patients had from one to six culture-positive sites. No colonized patient had positive cultures limited to the anterior nares.

Forty-six of 67 (69%) sites that were culture-positive for MRRSA in infected and colonized patients were either surgical wounds or respiratory tract sites.

Surveillance Cultures of Patients

The total number of patients who had case contact cultures was 326. Nine of 17 (53%) cases were identified by contact tracing. Of the cases identified by contact tracing cultures, five of nine (56%) were identified by the first set of cultures, three of nine (33%) were identified by the second set of cultures, and the remaining case (11%) was identified by the third set of cultures. Two hundred sixty-three patients were cultured during periodic surveillance culture surveys in high-risk areas (areas where cases had occurred earlier in the outbreak). Two of 17 (12%) cases were identified by surveillance cultures. Six of seventeen cases (35%) were discovered when the hospital laboratory isolated and identified MRRSA from clinical specimens.

Personnel Cultures

Between December 9, 1981 and March 11, 1982, a single set of cultures was obtained from each of 303 physicians and nursing personnel. Three of 203 (1.5%) nursing personnel were positive for MRRSA. The three nurses had MRRSA recovered from their anterior nares and hands simultaneously on at least one occasion. All 100 physicians had negative nasal and hand cultures for MRRSA. None of these persons had skin eruptions that would predispose to colonization with microorganisms, and none had skin infections due to MRRSA. The first two nurses were positive for MRRSA on initial cultures taken on February 9 and 16, respectively. These nurses worked in surgical intensive care units (General Surgery Intensive Care Unit and Neurosurgical Intensive Care Unit), and each cared for patients known to be positive for MRRSA. The third nurse was discovered to be a carrier of MRRSA several months after the outbreak was over. She had cared for a heavily colonized patient on a medical nursing unit.

Environmental Cultures

One thousand two hundred sixty-eight environmental cultures were taken from surfaces frequently in contact with the hands of patients and personnel. Sixteen cultures

TABLE 3
ANALYSIS OF TYPES OF INSTRUMENTATION AS RISK FACTORS FOR ACQUISITION OF MRRSA: ONE OCCURRENCE

Factor	Controls (Absent/Present)		Cases (Absent/Present)		Odds Ratio	*P*-Value
Tracheostomy	30	4	8	9	8.44	0.003*
Surgical operations	29	5	11	6	3.16	0.09*
Nasogastric tube	11	23	2	15	3.59	0.10*
Surgical drain	21	13	7	10	2.31	0.16†
Foley catheter	4	30	0	17	0.0	0.19*
Hemodialysis	30	4	17	0	0.0	0.19*
Ventilator support	9	25	2	15	2.70	0.20*
Peripheral IV	3	31	0	17	0.0	0.28*
Peritoneal dialysis	34	0	16	1	—	0.33*
Chest tube	23	11	10	7	1.46	0.53†
Arterial catheter	15	19	9	8	0.70	0.55†
Central IV	4	30	2	15	1.00	0.66*
Hyperalimentation	20	14	9	8	1.27	0.69†
Swan-Ganz catheter	23	11	11	6	1.14	0.83†
Endotracheal tube	10	24	5	12	1.00	1.00†

**Fisher's exact test (1-tail)*
†chi-square test

(1.26%) were positive for MRRSA. Surfaces culture-positive included telephones, a sphygmomanometer, a blood pressure cuff, a bed crank, a bedrail, an over bed light, a cabinet door handle, a chart cover, stethoscopes, an oxygen analyzer, a cardiac monitor, a plate stamping machine, a refrigerator door handle, and an isolation cart used for a colonized patient. In every case, patient care areas had been cultured following terminal cleaning after patients were transferred or discharged.

Air Cultures

Baseline samples of 30 cubic feet of air were taken at each of the three distances (4 feet, 12 feet, and 28 feet, see Figure 1) for each patient. In two instances one site served as the sample at 12 feet for one patient and as the sample at 28 feet for another patient; thus, there were ten samples taken. One colony of MRRSA was recovered from the 300 cubic feet of air sampled at baseline. After each manipulation, samples of 30 cubic feet were taken at 4 and 12 feet. No MRRSA were recovered from 240 cubic feet of air.

Case-Control Study

Results of the case-control study are shown in Tables 1-6. The eight cases of infection and nine cases of colonization were combined for the case-control study. Although cases and controls were not matched, there were no significant differences between cases and controls with respect to age, sex, race, duration of hospitalization prior to exposure, or duration of exposure. There was also no significant difference between cases and controls with respect to the distribution of patients among the specialty services (data not shown, $P = 0.34$, chi-square test).

Since the extent of underlying disease and the number of procedures and amount of instrumentation may have been interrelated, logistic regression analysis was performed to determine the relative importance of these risk factors. Due to the small number of cases, only two variables were included in the model for each analysis. When tracheostomy, power spray, or nasogastric tubes (≥ 2) were included with the number of diagnoses in the model, all three variables were more important than the number of diagnoses (Table 6). Inclusion of grouped procedures in the model revealed that surgical procedures and respiratory tract manipulations were more important than number of diagnoses. When included in the model, wound care manipulations were not significantly related to acquisition of MRRSA.

Antimicrobial therapy was not significantly related to whether a patient was a case or a control ($P = 0.74$, chi-square test).

Treatment of the Carrier State in Hospital Personnel

The first two nurses were removed from duty before treatment of their carrier state. The first nurse was treated for 10 days with topical bacitracin ointment. After therapy, nasal cultures were negative for MRRSA. One month later, he developed a purulent conjunctivitis due to MRRSA. The conjunctivitis cleared after treatment with topical bacitracin and gentamicin. Twenty-three cultures of his eye, nose, and hands over a 14-week period were all negative for MRRSA.

The second nurse was furloughed after cultures of nose and hands yielded MRRSA. Topical bacitracin was applied to the nose for 10 days. Post-treatment nasal cultures remained positive for MRRSA. After three additional positive cultures, she was treated with trimethoprim-sulfamethoxazole tablets and bacitracin ointment for 7 days. Cultures of anterior nares remained positive for MRRSA. She was then treated for 2 weeks with trimethoprim-sulfamethoxazole and topical bacitracin. This regimen also failed to eradicate the MRRSA carrier state. Two consecutive 2-week courses of 5% topical vancomycin were effective in eradicating MRRSA from her anterior nares. Twenty-three cultures over the next 3

TABLE 4
ANALYSIS OF TYPES OF INSTRUMENTATION AS RISK FACTORS FOR ACQUISITION OF MRRSA: TWO OR MORE OCCURRENCES

Factors	Controls (Absent/Present)		Cases (Absent/Present)		Odds Ratio	*P*-Value
Nasogastric tube	32	2	12	5	6.66	0.03*
Hyperalimentation	32	2	13	4	4.92	0.09*
Tracheostomy	33	1	14	3	7.07	0.10*
Peripheral IV	18	16	6	11	2.06	0.23†
Arterial catheter	31	3	14	3	2.21	0.31*
Swan-Ganz catheter	32	2	15	2	2.13	0.41*
Foley catheter	28	6	13	4	1.43	0.44*
Chest tube	32	2	17	0	0.0	0.44*
Central IV	25	9	12	5	1.16	0.53*
Surgical drain	21	13	9	8	1.43	0.54*
Endotracheal tube	29	5	14	3	1.24	0.54*
Ventilator support	9	25	4	13	1.17	0.55*
Surgical operations	23	11	12	5	0.87	0.83†

**Fisher's exact test (1-tail)*
†chi-square test

TABLE 5
GROUPED PROCEDURES AND INSTRUMENTATION AS RISK FACTORS FOR ACQUISITION OF MRRSA

Group	Controls Mean (SD)	Cases Mean (SD)	*P*-Value
Surgical procedures*	0.91 (0.90)	1.53 (1.18)	0.04#
Wound care†	9.58 (18.9)	28.4 (31.2)	0.03**
Respiratory tract‡	16.7 (21.1)	28.6 (22.8)	0.06#
Gastrointestinal tract§	0.91 (0.83)	1.11 (0.70)	0.38#
Skin punctures//	4.23 (2.30)	4.82 (2.51)	0.41#
Urinary tract¶	1.71 (2.73)	1.41 (0.94)	0.66**

* *Surgical procedures include surgical operations, peritoneal dialysis catheters, chest tubes, surgical drains, and tracheostomies.*
† *Wound care includes dressing changes, power spray, drain irrigation, and wound irrigation.*
‡ *Respiratory tract includes endotracheal tubes, suctioning, and ventilator support.*
§ *Gastrointestinal tract includes endoscopy and nasogastric tube.*
// *Skin punctures include hemodialysis, arterial catheters, Swan-Ganz catheters, central IV catheters, peripheral IV catheters, and hyperalimentation catheters.*
¶ *Urinary tract includes straight catheters, Foley catheters, and Foley catheter irrigation.*
\# *t-test.*
** *t-test (approximate for unequal variances).*

months were negative for MRRSA.

After the third nurse was discovered to be a nasal carrier of MRRSA, she was started on 5% topical vancomycin and treated for 2 weeks. Twenty-three cultures over the next 3 months were negative for MRRSA. Although the second nurse was initially removed from duty for treatment of the carrier state, both of the latter nurses were allowed to work in a non-surgical unit while being treated with topical vancomycin.

Microbiology

Results of tube dilution susceptibility tests are shown in Table 7. The MRRSA isolates were resistant to 18 of 21 antibiotics tested. Data on phage typing and plasmid typing are the subject of another report[19] but indicated that all isolates were of the same strain.

Control Measures

The key elements of our control measures were: 1) contact tracing with weekly cultures of all contacts of cases for the duration of their hospitalization or until they had had four negative sets of cultures; 2) extensive screening of clinical isolates by the hospital microbiology laboratory to identify new cases; 3) weekly surveillance cultures in high-risk areas where cases had been present in the past but where no known cases were present at the time the surveillance cultures were taken; 4) strict isolation of cases; 5) removal of personnel who were carriers from high-risk areas followed by treatment with topical antibiotics; 6) use of chlorhexidine in alcohol for decontamination of hands of personnel; 7) limited cohorting and restriction on movement of cases and contacts within the hospital; 8) in-service programs on proper isolation technique, handwashing, and the clinical significance of MRRSA; 9) decontamination of environmental surfaces in the room after each patient was discharged; and 10) flagging the medical records of cases for rapid identification and isolation on readmission.

DISCUSSION

To our knowledge this is the first report of an outbreak due to a rifampin- and methicillin-resistant strain of *Staphylococcus aureus*. However, this is not the first report of interstate transmission of MRSA. Such transmission was first reported by Saroglou and associates in 1980,[9] and this was followed 2 years later by the report of Locksley and coworkers.[20] In both of the latter outbreaks MRSA was transferred by burn patients, whereas our index case was a surgical patient transferred with vascular graft infection.

There appeared to be three possible reservoirs for MRRSA during the outbreak. First, as noted in previous

TABLE 6
RESULTS OF LOGISTIC REGRESSION ANALYSIS

Risk Factor	Intercept	Estimate	*P*-Value*	Fraction of Concordant Pairs
Individual				
Tracheostomy	−2.877	2.298	0.003	0.716
Number of diagnoses		0.685	0.055	
Power spray	−2.054	0.811	0.009	0.680
Number of diagnoses		0.290	0.415	
Nasogastric tube (≥2)	−2.492	2.176	0.024	0.623
Number of diagnoses		0.673	0.044	
Grouped				
Surgical procedures	−0.195	2.418	0.0008	0.822
Number of diagnoses		−0.431	0.275	
Respiratory tract	0.491	1.162	0.004	0.779
Number of diagnoses		−0.380	0.272	
Wound care	1.473	1.120	0.119	0.648
Number of diagnoses		−0.401	0.226	

**chi-square test*

outbreaks due to MRSA,[4,6,7,20] one reservoir was made up of patients colonized or infected with MRRSA. Second, two of the three personnel who were nasal carriers may have constituted another reservoir. Other investigators have also identified nasal carriers among hospital staff during outbreaks of MRSA infection.[2,4,6-8,10,13-15,20,21,23,24] Third, except for outbreaks among burn patients,[6,9,22] most investigators have failed to recover MRSA from the environment of patients.[4,8,10,13,14,21] The extent of environmental contamination during our outbreak was difficult to determine since cultures were taken following terminal cleaning of environmental surfaces after patients were transferred or discharged. However, the observation that the environmental surfaces culture-positive for MRRSA were those in frequent contact with hands of personnel suggests that the environment may have been one reservoir for the epidemic strain.

The most likely mode of transmission of MRRSA during our outbreak was cross-contamination between patients by direct contact with the contaminated hands of personnel. Although most of the nurses and all of the physicians had negative hand cultures, positive cultures from hands of personnel have been noted in three previously reported outbreaks.[6,7,25] It is possible that we would have recovered MRRSA from the hands of personnel other than the nasal carriers if we had taken more cultures.

The role that hospital personnel who are colonized or infected with MRSA play in transmitting MRSA during an outbreak has not been firmly established. However, in five outbreaks transmission of MRSA to patients was epidemiologically linked to carriers among hospital personnel.[10,13,14,20,21] Although the two nurses discovered late in the outbreak to be nasal carriers of MRRSA could not be directly implicated in transmission of MRRSA to patients, they were the only personnel who had hand cultures positive for MRRSA. Of further interest is the observation that cultures of hands and anterior nares taken simultaneously were both positive in each of the three staff members and that none of these nurses had skin lesions or dermatitis on their hands. Two of the three worked in intensive care units where most of the MRRSA cases occurred. However, it is also possible that the nurses became colonized late in the outbreak and played little or no role in transmission of MRRSA to patients.

Our data would indicate that MRRSA were not transmitted between patients by the airborne route. In most

TABLE 7
ANTIBIOTIC SUSCEPTIBILITY TESTS FOR ISOLATES* OF MRRSA TO 21 ANTIBIOTICS

Antibiotic	Minimal Inhibitory Concentration (μg/ml)	Minimal Bactericidal Concentration (μg/ml)
Amikacin	25->100	25->100
Ampicillin	>100	>100
Bacitracin	0.195-0.78	0.195-3.125
Carbenicillin	≥100	≥100
Cefazolin	25-100	50-≥100
Cefoxitin	12.5-100	12.5-100
Chloramphenicol	100	>100
Clindamycin	>100	>100
Cycloserine	25-50	50-100
Doxycycline	12.5-50	≥100
Erythromycin	>100	>100
Gentamicin	>100	>100
Minocycline	6.25-12.5	12.5-≥100
Moxalactam	25-50	25-≥100
Nafcillin	12.5-25	25->100
Penicillin	≥100	≥100
Piperacillin	50-100	≥100
Tetracycline	12.5-100	25-100
Trimethoprim/ sulfamethoxazole	2/38	2/38
Troleandomycin	>100	>100
Vancomycin	0.39-1.56	0.39-3.125

**Fourteen to 16 isolates were tested with each antibiotic.*

outbreak investigations during which air samples were taken few or no samples contained MRSA,[4,7,14,21] and in the one outbreak where 50% of samples were positive[6] no evidence was presented that could establish transmission of MRSA between patients by way of the air.

Our case-control study differed in several important ways from previously published studies. First, unlike four of the previously reported case-control studies,[5,7,14,20] we did not use matched controls. However, there were no significant differences between our cases and controls with respect to age, sex, race, duration of hospitalization prior to exposure or duration of exposure. Second, five of the earlier studies compared patients with infections due to MRSA with patients with infections due to methicillin-sensitive *S aureus*.[5,7,14,20,26] We compared patients culture-positive for MRRSA (infected or colonized) with patients culture-negative for MRRSA. We wished to define risk factors for acquisition (infection or colonization) of MRRSA in the patient population in the area of the hospital where the outbreak occurred instead of comparing our cases with a very select population (patients colonized or infected with methicillin-sensitive *S aureus*). Third, in none of the previously published case-control studies[5,7,10,14,20,26] was there any mention of whether cases and controls were exposed to patients culture-positive for MRSA continuously or intermittently and whether or not periods of actual exposure were taken into account when data on potential risk factors were extracted from case records.

We observed that the number of secondary diagnoses (underlying diseases) and total number of diagnoses were significantly related to acquisition of MRRSA. In only one previous study[26] did the authors examine the relationship between total number of diagnoses and infection with MRSA. Similar to our findings, they noted a significant relationship between the mean number of associated diseases and whether or not the patient developed an infection with MRSA. Combining all diagnoses may provide a measure of the degree of chronic illness and debilitation.

We studied many procedures and types of instrumentation in an attempt to identify risk factors for acquisition of MRRSA. Most of the manipulations significantly related to acquisition of MRRSA were associated with surgical wounds and the respiratory tract. The power spray procedure was used to debride and irrigate wounds postoperatively. Tracheostomy was both a surgical operation and a type of instrumentation of the respiratory tract. Prolonged nasogastric intubation (two or more nasogastric tubes) provided for extensive manipulation and contact with the nasopharynx. Although of borderline significance, endotracheal suctioning also involved manipulation of the upper respiratory tract. When potential risk factors were grouped into six categories, surgical procedures and wound care were significantly associated with acquisition of MRRSA and instrumentation of the respiratory tract was of borderline significance.

It was considered possible that the degree of illness (number of diagnoses) and whether a patient had certain types of procedures and instrumentation might be related. However, logistic regression analysis indicated that tracheostomy, power spray, and prolonged nasogastric intubation were independent of degree of illness. When logistic regression analysis was performed with the grouped procedures, it was also found that surgical procedures and respiratory tract manipulations were independent of degree of illness. When wound care manipulations were included in the model with number of diagnoses, wound care was no longer significantly related to acquisition of MRRSA. However, association of surgical procedures, power spray and respiratory tract manipulations with the cases is consistent with the observation that most cases had infection or colonization with MRRSA either in a surgical wound or the respiratory tract. The association of tracheostomy, power spray, surgical procedures and respiratory tract manipulations with acquisition of MRRSA is further strengthened by the higher fractions of concordant pairs for those variables.

Only two of the published case-control studies examined a large number of procedures in an attempt to identify risk factors for infection with MRSA. In the first study, Ward and associates[10] observed a significant relationship between the total number of invasive procedures and infection with MRSA. In the second study, Lentino and coworkers[26] investigated an outbreak of pneumonia due to MRSA. It was noted that cases were significantly more likely than controls to have had intravascular devices, endotracheal intubation, indwelling catheters, surgery and ventilatory support. It is not clear whether cases and controls in the latter studies were exposed throughout their course of hospitalization or for only some portion of this period. In both studies case patients had more severe illnesses and were hospitalized for longer periods than controls. This could have been associated with more instrumentation in the case patients. If cases were not exposed to MRSA throughout their hospitalization, many of the invasive procedures recorded may have occurred at times when cases were not at risk for infection with MRSA and could, therefore, not be considered risk factors. Although our estimates of the periods of exposure of our cases and controls may not have been precise in every instance, our approach would likely have provided a more accurate assessment of risk factors for acquisition of MRRSA than one in which invasive procedures were tabulated throughout hospitalization without regard to whether they occurred during periods of exposure of case and control patients.

We found no relationship between administration of antibiotics and acquisition of MRRSA. This is in contrast to five previously published case-control studies[5,7,14,20,26] in which significant differences were noted in prior administration of antibiotics to cases and controls. The difference between our findings and those of previous investigators may be due to the longer period between admission and first positive cultures for cases as compared to controls in the earlier studies.

Our control measures limited the outbreak to eight cases of infection and nine cases of colonization over 8 months. Although limited cohorting was instituted, the cornerstone of our control measures was rapid identification of new cases by contact tracing using a selective medium to culture all body sites that might harbor MRRSA. Control measures were rapidly effective even though the outbreak strain was a highly resistant strain of MRSA including resistance to rifampin. Cases not identi-

fied by contact tracing were uncovered by surveillance cultures in high-risk areas and by screening of clinical isolates in the hospital laboratory. Although Thompson and coworkers[25] performed surveillance cultures and monitored the clinical microbiology laboratory on a daily basis, they did not do contact tracing. As shown by our data, contact tracing was the most effective technique for identifying new cases in our hospital. Contact tracing also minimized the period of time that a new case could be a source of MRRSA for colonization or infection of other patients.

Treatment of personnel who were nasal carriers of MRRSA may have been another important control measure. First, nasal carriers were the only personnel who had hand cultures positive for MRRSA. Second, cultures taken of nose and hands simultaneously were positive. In the absence of skin lesions on the hands this suggests that the carriers were contaminating their hands from their noses.

In previous reports of MRSA outbreaks nasal carriers have been treated with bacitracin ointment with[13,21] or without[14] hexachlorophene showers with variable success. In one outbreak nasal carriers were treated successfully with chlorhexidine cream.[9] We could not use the regimen of Ward and associates,[10] because our epidemic strain was resistant to rifampin. To our knowledge, our outbreak was the first in which MRSA was eradicated from the anterior nares of carriers by topical vancomycin.

We are uncertain of the importance of the remaining control measures except for flagging case patients' charts at the time of discharge. This provided for immediate recognition and isolation on readmission. These patients were frequently readmitted and most were still carrying MRRSA when rehospitalized.

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