Effectiveness of Contact Isolation during a Hospital Outbreak of Methicillin-resistant Staphylococcus aureus

John A. Jernigan,1 Maureen G. Titus,1 Dieter H. M. Gröschel,1 Sandra I. Getchell-White,1 and Barry M. Farr1

Contact isolation has been recommended by the Centers for Disease Control and Prevention for the prevention of nosocomial transmission of methicillin-resistant Staphylococcus aureus (MRSA), but there are few data which prospectively quantitate the effectiveness of contact isolation for this purpose. During an outbreak of MRSA in a neonatal intensive care unit between July 18, 1991 and January 30, 1992, weekly surveillance cultures were performed on all patients. Sixteen of 331 admissions became colonized with MRSA, and 3 (19%) developed infections: bacteremia, conjunctivitis, and dialysis catheter site infection. The isolates from all 16 patients were submitted to plasmid profile analysis and restriction enzyme analysis of whole cell DNA. All of the patients had identical chromosomal patterns and plasmid profiles, which differed from control isolates from other wards, indicating that the outbreak resulted from spread of a unique strain. None of 144 personnel who were cultured after recent contact with newly colonized patients during the outbreak were found to carry MRSA, which suggests that patients were the reservoir for transmission rather than caregivers. The most probable source for each individual transmission was determined based on proximity in time and space and shared exposure to caregivers. The rate of transmission of MRSA from patients on contact isolation was significantly lower (0.009 transmissions per day on isolation) than the rate for patients not on isolation (0.140 transmissions per day unisolated, relative risk = 15.6, 95% confidence interval 5.3-45.6, p < 0.0001). The authors conclude that the risk of nosocomial transmission of MRSA was reduced 16-fold by contact isolation during the outbreak in this neonatal intensive care unit. These data confirm the results of previous studies which have suggested that contact isolation was effective in controlling the epidemic spread of methicillin-resistant Staphylococcus aureus. Am J Epidemiol 1996;143:496-504.

Staphylococcus aureus resistant to methicillin (MRSA) has become an increasingly important nosocomial pathogen in US hospitals. Data from the National Nosocomial Infection Surveillance System (NNIS) show that the proportion of S. aureus isolates resistant to methicillin has increased from 2 percent to 29 percent in NNIS hospitals during the last 15 years (1). MRSA has spread rapidly in many hospitals, causing substantial morbidity and mortality (2). Although methicillin-resistant and methicillin-sensitive strains of S. aureus (MSSA) have had similar virulence in animal models (3), one prospective study demonstrated a significantly greater risk of staphylococcal infection in patients colonized with MRSA compared with those colonized with MSSA (4). Some investigators have reported that increasing rates of MRSA infection have increased the total endemic rate of S. aureus infections rather than merely replacing an equal number of methicillin-sensitive S. aureus infections (5-7), although other investigators have not confirmed this finding (8, 9). There is concern that vancomycin use may increase substantially as MRSA becomes more prevalent, resulting in increased selection pressure for vancomycin-resistant organisms (10). For these reasons, many believe that efforts to control MRSA are warranted (2, 10, 11). A recent survey of US hospital epidemiologists (2) found that 91 percent of the epidemiologists used MRSA control measures of some kind in their hospitals.

Although barrier precautions are often included in recommended control measures for MRSA (2, 10-12), and are used by 76 percent of US hospitals (2), the data on their effectiveness are conflicting. While some studies have found a decrease in the incidence of
endemic MRSA infection/colonization after adopting barrier isolation procedures (8, 9, 13, 14), others have failed to demonstrate a change in incidence using the same or similar measures (15–17). To our knowledge, no study has directly compared the rate of transmission of MRSA from unisolated patients with the rate of transmission from patients who have been placed in contact isolation.

During a 7-month outbreak of MRSA in a neonatal intensive care unit in Charlottesville, Virginia, prospective culturing and epidemiologic analysis allowed measurement of transmission rates from unisolated patients for comparison with the transmission rates from patients who were in contact isolation.

MATERIALS AND METHODS

Description of the hospital and neonatal intensive care unit

The University of Virginia Hospital is a 700-bed hospital with nine intensive care units. The hospital provides primary and tertiary care, and admits over 28,000 patients annually. The neonatal intensive care unit (NICU) has 33 beds and admits approximately 700 neonates each year. The unit consists of four pods containing 6–10 beds each, and an isolation room containing an anteroom and two beds. One nurse generally cares for two infants during a single shift. When a nurse leaves the unit during the shift, the nurse for an adjacent patient will observe and provide emergent care if needed. The pods are separated by partitions interrupted by walkways through which personnel pass from one pod to the other.

Routine MRSA control measures

The hospital infection control team, which consisted of a hospital epidemiologist and four full-time infection control practitioners, conducted prospective surveillance twice weekly within the unit using the Kardex method (18). Clinical microbiology laboratory results were monitored daily for isolates of MRSA from any site. All patients colonized or infected with MRSA were placed in contact isolation (12). This consisted of wearing a mask when within 5 ft (1.5 m) of the patient, a gown for direct contact with the patient, and gloves for manual contact with the patient or any other potentially contaminated surfaces. Contact isolation was maintained until the time of discharge from the hospital or eradication of colonization had been documented. Roommates and other nearby patients considered at risk were cultured to detect MRSA colonization. Whenever positive results were found, the area of surveillance was widened to assure that additional undetected cases were not present. Surveillance cultures for detecting colonization were obtained from the nose, axilla, and groin and, also, from the site of any percutaneous device or skin wound.

Outbreak control measures

When the outbreak began, four additional control measures were instituted:

1. Weekly surveillance cultures were obtained of the nares, groin, axilla, and wounds (if present) on all patients in the unit not previously known to be colonized or infected with MRSA.
2. Staff compliance with control measures, including diligent hand washing with chlorhexidine soap, was repeatedly encouraged through discussions with unit personnel and memoranda.
3. For selected patients, attempts at eradication of colonization were made. Eradication regimens were selected by the patient’s primary physician. Eradication was defined by three consecutive daily cultures (nares, groin, axilla, wound, and any other site known to be previously colonized) beginning at least 72 hours after discontinuation of antibiotics. Culture surveillance of previously colonized patients was continued until hospital discharge with four consecutive weekly cultures, followed by monthly cultures.
4. Surveillance cultures were obtained from personnel who had had contact with new cases during the 2 weeks preceding identification of a case by conversion of surveillance cultures from negative to positive. Cultures were obtained from the nares and any visible skin lesions of personnel.

Molecular typing of isolates

Plasmid profile analysis was performed after rapid alkaline lysis of staphylococci according to Birnboim and Doly (19) with the Kloos modification (20) of substituting lysozyme with lysostaphin (100 μg/ml) and including a −70°C freezing cycle in the extraction step. Restriction enzyme fingerprinting of whole-cell deoxyribonucleic acid (DNA) was performed according to the method of Bialkowska-Hobrzanska et al. (21).

Epidemiologic studies

The probable source for each transmission was identified through analysis of the following parameters: 1) temporal relation between proposed source and recipient; 2) geographic relation between proposed source and recipient; and 3) personnel shared between the proposed source and recipient. The analysis was performed independently by two observers.
Using prospective weekly culture results, the approximate day of acquisition of MRSA was determined for each patient. Because surveillance cultures were obtained every 7 days, patients acquired MRSA at some point between day 1 and day 7 following their last negative culture. Acquisition was estimated to have occurred at the midpoint of that interval, i.e., day 3.5. For patients exposed to a known source at some time following their last negative culture, the date of acquisition was estimated as the midpoint between first exposure to the source and their first positive culture. The end of the period of colonization within the unit was defined as the date of discharge from the unit or, if eradication attempts were successful, the midpoint between initiation of eradication therapy and the initiation of cultures that documented eradication.

**Microbiology**

*Staphylococcus aureus* was identified by standard laboratory procedures (22). The determination of methicillin-resistance was performed according to the methods recommended by the National Committee on Clinical Laboratory Standards for disk diffusion testing (23), and the use of an oxacillin salt agar screening plate (24).

**Statistical methods**

Rates were compared using the large-sample test for comparison of incidence rates (25). Confidence intervals for simple proportions were determined using published tables of exact confidence limits for binomial distributions (26).

**RESULTS**

**Description of the outbreak**

In the 5 years preceding this outbreak, only four sporadic nosocomial cases of MRSA colonization or infection had been identified in the neonatal intensive care unit. The outbreak occurred during the 7-month period between July 18, 1991 and January 30, 1992 (figure 1). The index case was identified through an eye culture of an infant with purulent conjunctivitis on July 18, 1991. This patient had recently traveled out of the NICU for a surgical procedure in the operating room and was being followed by a non-NICU surgical consultation team. Over the next week, four additional cases were identified that were epidemiologically linked to the index case (figure 2). Outbreak control measures, including weekly surveillance cultures of all patients in the unit who were not known to be previously colonized, were begun on July 30, 1991. Over the next 6 months, 11 new colonizations or infections were detected. By October 28, 71 days into the epidemic, there was only one remaining case in the NICU isolation room. This case remained the only reservoir in the unit for the ensuing 5 weeks before the next transmission was detected. Surveillance cultures at the end of that 5-week period revealed MRSA coloniza-
FIGURE 2. Methicillin-resistant *Staphylococcus aureus* (MRSA) transmissions depicted in space and time in an outbreak in a neonatal intensive care unit, Charlottesville, Virginia, 1991–1992. Five floor plans of the neonatal intensive care unit are shown. Each floor plan corresponds to a time period during which transmissions occurred. Arrows indicate the donor and recipient of each transmission. Dates indicate when cultures were recognized to be growing MRSA.

tion of three new babies located a considerable distance from the isolation room. The only personnel who had shared care for the isolated baby and the others were the attending and resident physicians. One of the first-year residents, who reportedly had more manual contact with the babies than the other physicians, had been primarily responsible for case 8 in the isolation room and also for new cases 12 and 13 (figure 2). At least one colonized or infected infant remained in the unit until April 27, 1992 (figure 1). Weekly surveillance cultures of every infant in the unit was continued for another 2 weeks, and no new cases were identified during that period.

Five months after the final transmission of the outbreak and 6 weeks after discharge of the final patient reservoir from the NICU, two new cases of MRSA colonization with the outbreak strain were identified in adjacent beds within the unit. One of these patients had been admitted to the unit following discharge of the last patient reservoir, and the patient developed MRSA infection of a surgical wound. The other patient had been present in the unit during the period when there were other patient reservoirs present, but was culture-negative for MRSA for the duration of weekly surveillance of the unit. Because no patient reservoir existed in the unit at the time of acquisition, extensive surveillance culturing of personnel was repeated. Two nurses were found to be colonized with MRSA. One of these nurses (Nurse A) was epidemiologically linked to the new cases. Nurse A had worked with the last colonized infant in the isolation room of the unit. She was found to be colonized with the outbreak strain in the groin and at the site of an eczematous lesion on her hand. This nurse had been cultured during the outbreak and was negative at that time. The other nurse (Nurse B), who had not worked with any of the previous MRSA cases, worked with the two new cases after Nurse A and prior to their being isolated; she was colonized in the nares only. The nurses’ colonization was eradicated, as shown in table 1. The infants were placed on contact isolation and discharged within 3 weeks, and weekly surveillance cultures of all patients were continued for an additional 3 weeks following their discharge with no positive results. No further cases of MRSA colonization or infection were observed in the ensuing 44 months.

Description of the patients

During the 7 months, 16 (4.8 percent) of 331 neonates admitted to the unit acquired MRSA. The most common diagnoses among patients with MRSA infection or colonization were prematurity (87 percent), patent ductus arteriosus (44 percent), pneumonitis/ respiratory distress syndrome (25 percent), and intraventricular hemorrhage (19 percent). Thirteen of the cases were colonized and three were infected. In addition to the index case (conjunctivitis), the infections included a Tenckhoff dialysis catheter site infection and one bacteremia. All three infections were successfully treated with vancomycin. The most common sites of colonization were nares (88 percent), umbilicus (56 percent), groin (50 percent), and axilla (31 percent).

Results of personnel cultures

None of the 144 personnel cultures taken during the outbreak were positive for MRSA. During the investigation of the two cases which appeared after the resolution of the outbreak, two (1.1 percent) of 181 personnel were found to be colonized.

Outcome of eradication regimens

Ten patients received therapy to eradicate colonization and had evaluable outcome data. Eradication was successful in seven of the 10 patients. The regimens used and duration of follow-up are detailed in table 1.

Molecular typing

All 16 isolates had identical restriction fragment profiles for total cellular DNA which clearly differed from control MRSA isolates obtained from other wards (figure 3). All 16 isolates contained a single plasmid of identical molecular weight, which differed significantly from the control isolates. The isolates from the two patients and two personnel which were discovered following resolution of the outbreak had DNA restriction fragment length and plasmid profiles identical to the original outbreak isolates and different from controls.

Epidemiologic studies

There were 629.5 patient-days of MRSA colonization during the outbreak. A total of 558 patient-days of colonization were spent in contact isolation, and 71.5 patient-days of colonization were not spent in contact isolation (table 2). In all, there were 15 transmissions, giving a total rate of 0.17 transmissions per colonized patient-week during the outbreak.

The results of epidemiologic tracing of the source of the transmission by two independent observers were 100 percent concordant. Unisolated infants were judged to be the source of 10 transmissions, while isolated infants were believed to be responsible for five transmissions (table 2).
The relative risk of transmission from unisolated patients was 15.6 compared with patients on contact isolation (table 3).

DISCUSSION

The majority of the published literature supports the concept that colonized patients are the major reservoir for MRSA and that most transmissions occur via the hands of hospital personnel. Although several studies have examined the effect of isolation procedures in controlling nosocomial transmission of MRSA, the results have not been consistent (13–17, 27). Some studies found a decrease in the incidence of endemic MRSA infection/colonization after adopting barrier isolation procedures, including one study conducted at the University of Virginia Hospital more than a decade ago (8, 9, 13, 14). Others have failed to demonstrate a change in incidence with the use of the same or similar isolation procedures.


<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sites colonized</th>
<th>Regimen (duration)</th>
<th>Outcome</th>
<th>Follow-up (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nares</td>
<td>Nasal mupirocin (14 days), vancomycin (7 days), rifampin (4 days)</td>
<td>Eradicated</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>Nares, axilla, groin, umbilicus</td>
<td>Nasal mupirocin (2 days)</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Nares, umbilicus, urine</td>
<td>Nasal + umbilical mupirocin (3 days)</td>
<td>Eradicated</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>Nares, axilla, groin, umbilicus</td>
<td>Nasal + umbilical mupirocin (7 days), vancomycin (14 days), removal of dialysis catheter</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Nares, axilla, groin, umbilicus</td>
<td>Nasal + umbilical mupirocin (14 days), vancomycin (14 days)</td>
<td>Eradicated</td>
<td>31</td>
</tr>
<tr>
<td>12</td>
<td>Nares, groin, sputum, tracheostomy</td>
<td>Nasal + tracheostomy mupirocin (14 days), rifampin (14 days), TMP/SMX* (14 days), chlorhexidine baths (14 days), change tracheostomy tube (day 7)</td>
<td>Eradicated</td>
<td>80</td>
</tr>
<tr>
<td>13</td>
<td>Nares, axilla, groin, umbilicus</td>
<td>Nasal mupirocin (14 days), chlorhexidine baths (14 days)</td>
<td>Eradicated</td>
<td>11</td>
</tr>
<tr>
<td>14</td>
<td>Nares</td>
<td>Nasal mupirocin (14 days)</td>
<td>Relapse at 18 days</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Nares, umbilicus</td>
<td>Nasal + umbilical mupirocin (13 days)</td>
<td>Eradicated</td>
<td>14</td>
</tr>
<tr>
<td>16</td>
<td>Nares</td>
<td>Nasal + gastrostomy tube mupirocin (12 days)</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Nares, axilla, groin, umbilicus, gastrostomy tube</td>
<td>Nasal + gastrostomy tube mupirocin (14 days), change gastrostomy tube</td>
<td>Failed</td>
<td></td>
</tr>
<tr>
<td>Nurse A</td>
<td>Hand, groin</td>
<td>Rifampin (10 days), TMP/SMX (10 days)</td>
<td>Eradicated</td>
<td>67</td>
</tr>
<tr>
<td>Nurse B</td>
<td>Nares</td>
<td>Nasal mupirocin (10 days)</td>
<td>Eradicated</td>
<td>76</td>
</tr>
</tbody>
</table>

* TMP/SMX, trimethoprim/sulfamethoxazole.

measures (15–17). Murray-Leisure et al. (15) found that contact isolation alone failed to control an epidemic in their hospital. It was only after intensifying their surveillance efforts and aggressive cohorting of personnel that they observed a decline in the incidence of MRSA colonization. Reboli et al. (17) reported that contact isolation failed to control an MRSA epidemic in a neonatal intensive care unit until the initiation of hexachlorophene handwashing. Rao et al. (16) also observed that contact isolation failed to limit the spread of an MRSA outbreak, but strict isolation was successful in doing so. The only controlled study of types of isolation for MRSA compared strict isolation with modified contact isolation and failed to detect a significant difference in rate of transmission, but the study included only 20 cases and had only 23 percent power to detect a 50 percent relative reduction in rate. In this 7-month outbreak in a neonatal intensive care unit, a combination of infection control measures, including contact isolation, effectively controlled epidemic spread of a single strain of MRSA. Transmission of MRSA was 16 times more frequent from unisolated patients during the outbreak than from patients in contact isolation.

The determination of comparative rates of transmission in this study depended on identification of the source for each transmission. Although errors in identification of the source could have altered the results, such errors were unlikely since two independent observers reached identical conclusions. Furthermore, in the unlikely event that errors were made, the final conclusions would not have been significantly affected. For example, even if five of the 10 transmissions attributed to unisolated infants had been misclassified (i.e., the transmissions actually originated from isolated patients), the rate of transmission from unisolated infants would have remained significantly higher than from isolated infants (relative risk = 4.7, 95 percent confidence interval 1.6–13.8).
It should be noted that MRSA colonization was eradicated from seven of the 10 patients in whom this was attempted, including patient no. 8. Eradication of MRSA from these seven colonized patients may have played an important role in controlling this outbreak. The potential importance of eradicating colonization may be best illustrated by the consequences of a delay in attempting eradication for patient no. 8, one of the colonized patients. This patient remained colonized for 2 1/2 months before eradication was attempted and was the only remaining reservoir for MRSA in the unit for a period of 5 weeks. Had the eradication of MRSA been begun earlier during hospitalization for patient no. 8, it appears that the last five cases of the outbreak could have been prevented, as well as the colonization of two nurses and the occurrence of two more cases 5 months after the last case of the outbreak. Earlier eradication of S. aureus in patient no. 8 would thus have obviated the need for up to 6 months isolation and weekly surveillance cultures and also for hundreds of surveillance cultures of personnel.

The absence of detectable colonization among personnel during the outbreak suggests that patients rather than health care workers served as the major reservoir for transmission. Similar observations have been recorded in the majority of published MRSA outbreaks (2, 10). Health care workers have been identified as a reservoir of MRSA colonization in some reports, but in a majority of these outbreaks, the implicated individuals had colonization of the hands or areas of dermatitis rather than nasal colonization alone (2). A nurse (Nurse A) apparently served as the reservoir for transmission to two patients who became colonized following the outbreak. This nurse, who was colonized at the site of an eczematous hand lesion and groin, had cared for these two patients after caring for the final colonized infant of the outbreak 6 weeks earlier. Nurse A had had negative cultures of the nares during the outbreak and no visible lesions of eczema at that time. Only two infants became colonized despite the fact that Nurse A worked with multiple patients during the 6-week period following discharge of the last colonized infant of the outbreak, perhaps due to use of gloves and regular use of chlorhexidine handwash.

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REFERENCES


