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Jad Khoury
Washington University School of Medicine in St. Louis

Marilyn Jones
Washington University School of Medicine in St. Louis

Autumn Grim
Washington University School of Medicine in St. Louis

Wm. Michael Dunne Jr.
Washington University School of Medicine in St. Louis

Vicky Fraser
Washington University School of Medicine in St. Louis

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Author(s): Jad Khoury , MD, Marilyn Jones , RN, CIC, Autumn Grim , MPH, Wm. Michael Dunne , Jr., PhD, Vicky Fraser , MD
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ERADICATION OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* FROM A NEONATAL INTENSIVE CARE UNIT BY ACTIVE SURVEILLANCE AND AGGRESSIVE INFECTION CONTROL MEASURES

Jad Khoury, MD; Marilyn Jones, RN, CIC; Autumn Grim, MPH; Wm. Michael Dunne, Jr., PhD; Vicky Fraser, MD

ABSTRACT

OBJECTIVES: To describe an outbreak of hospital-acquired MRSA in a NICU and to identify the risk factors for, outcomes of, and interventions that eliminated it.

SETTING: An 18-bed, level III–IV NICU in a community hospital.

METHODS: Interventions to control MRSA included active surveillance, aggressive contact isolation, and cohorting and decolonization of infants and HCWs with MRSA. A case–control study was performed to compare infants with and without MRSA.

RESULTS: A cluster of 6 cases of MRSA infection between September and October 2001 represented an increased attack rate of 21.2% compared with 5.3% in the previous months. Active surveillance identified unsuspected MRSA colonization in 6 (21.4%) of 28 patients and 6 (5.5%) of 110 HCWs screened. They were all successfully decolonized. There was an increased risk of MRSA colonization and infection among infants with low birth weight or younger gestational age. Multiple gestation was associated with an increased risk of colonization (OR, 37.5; CI_{95}, 3.9–363.1) and infection (OR, 5.36; CI_{95}, 1.37–20.96). Gavage feeding (OR, 10.33; CI_{95}, 1.28–83.37) and intubation (OR, 5.97; CI_{95}, 1.22–29.31) were associated with increased risk of infection. Infants with MRSA infection had a significantly longer hospital stay than infants without MRSA (51.83 vs 21.46 days; $P = .003$). Rep-PCR with *mec* typing and PVL analysis confirmed the presence of a single common strain of hospital-acquired MRSA.

CONCLUSION: Active surveillance, aggressive implementation of contact isolation, cohorting, and decolonization effectively eradicated MRSA from the NICU for 2½ years following the outbreak (*Infect Control Hosp Epidemiol* 2005;26:616-621).

Several outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in neonatal intensive care units (NICUs) have been described since the early 1980s. Efforts to eradicate and control MRSA colonization and infection have had variable degrees of success and recurrences of MRSA outbreaks have been described.[1] Haley et al. illustrated the difficulties encountered with controlling a MRSA outbreak in their NICU that lasted more than 3 years.[2] On the other hand, Farrington et al. reported the success of simple control measures to restrict the spread of MRSA in a special care baby unit.[3] Implementation of MRSA control efforts in NICUs has been hindered by additional factors such as overcrowding and limited space.[4] Despite variable outcomes of MRSA control measures, early recognition of outbreaks and institution of aggressive infection control measures have been shown to be cost-effective.[5,6]

We describe the successful eradication of a hospital-acquired strain of MRSA from a NICU and the infection control methods used to halt an outbreak that had been going on for months, as well as the risk factors for and outcomes of infection or colonization with MRSA. This study describes the effects of active surveillance and aggressive infection control measures in successfully terminating a MRSA outbreak in the NICU of a community hospital.

METHODS

Setting

The medical center is a community hospital with 300 beds, and the NICU is a level III–IV unit with 18 beds that has an average of 170 admissions per year and an estimated census of 10 to 12 patients daily. The NICU is divided into two large rooms designated room 1 and room 2. These rooms are further divided into a total of 5 sections, each with 2 to 5 beds used for routine admissions; room 1 has an additional section with 3 isolation beds.

Outbreak

A cluster of six cases of MRSA infection were identified in the NICU from early September 2001 to mid-Octo-

Drs. Khoury and Fraser are from the Department of Internal Medicine, Division of Infectious Diseases; Ms. Jones and Ms. Grim are from the BJC Infection Control and Healthcare Epidemiology Consortium; and Dr. Dunne is from the Department of Microbiology, Washington University School of Medicine, St. Louis, Missouri.

Address reprint requests to Victoria Fraser, MD, Infectious Diseases Division, Washington University School of Medicine, Box 8051, 660 S. Euclid Ave., St. Louis, MO 63110. vfraser@im.wustl.edu

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ber 2001, representing an increase in the incidence of MRSA compared with the previous year. A review of the infection control policies and procedures for the NICU was performed, and changes and remedies were introduced where necessary to control the spread of MRSA and prevent future outbreaks. Infection control nurses ensured the proper application of infection control measures.

Cultures and Microbiology

Routine surveillance of all clinical cultures positive for MRSA throughout the hospital had been used by infection control to monitor the incidence of nosocomial MRSA infections. This routine surveillance identified the cluster of 6 cases in the NICU and prompted the institution of active culture surveillance on October 14, 2001. Samples for screening cultures for MRSA were obtained by swabbing the periumbilical and perirectal areas of all of the infants present in the NICU on October 14, 2001, and all newly admitted patients until the end of January 2002. These surveillance cultures for MRSA were repeated weekly. A total of 28 infants were screened. In addition, samples for screening cultures were obtained once from the anterior nares of 110 healthcare workers (HCWs) working in the NICU. Those who were colonized with MRSA underwent 3 repeat nasal cultures on a weekly basis after receiving decolonization treatment to document clearance and identify persistent carriage.

The identification of MRSA from screening cultures was performed using oxacillin salt agar plates according to the methods recommended by the National Committee for Clinical Laboratory Standards.[7] All MRSA isolates obtained from NICU patients and HCWs from September 1, 2001, through January 2002 were saved for molecular typing and analysis of the SCC*mec* cassette and Panton–Valentine leukocidin.

Infection Control Measures

A unit-wide cleaning with routinely used quaternary ammonium disinfectants took place at the beginning of the outbreak in October 2001, but no environmental cultures were performed. NICU infants who were infected or colonized with MRSA were placed in contact isolation and cohorted geographically. Infection control nurses directly observed HCWs and educated them about proper contact isolation techniques and the importance of meticulous hand hygiene, emphasizing handwashing with soap or alcohol-based foam before and after every patient contact. Visible signs were placed on the beds of infected or colonized patients to remind the NICU staff and patients' families about the need for contact isolation and hand hygiene. Contact isolation required the use of barrier precautions such as gloves, gowns, and sometimes masks for all direct patient contact.

Decolonization

Colonized patients received mupirocin ointment twice daily to the anterior nares and umbilical area for 7 days. HCWs who had a nasal culture positive for MRSA took a hexachlorophene shower daily and received the following twice daily for 1 week: 600 mg of rifampin orally, one double-strength tablet of trimethoprim–sulfamethoxazole orally, and mupirocin ointment to the anterior nares.

Molecular Typing

Repetitive sequence polymerase chain reaction (PCR) genotyping was used to study the clonality of the MRSA isolates. DNA isolation and amplification with RW3A primer were performed as previously described by Del Vecchio et al.[8] PCR products underwent electrophoresis in a 1.5% agarose gel (Type 1-A, Sigma Chemical Co., St. Louis, MO), were stained in 5 μg/mL of ethidium bromide, and were visualized using the Gel Doc 1000 system and Molecular Analyst software (Bio-Rad Laboratories, Hercules, CA). Banding patterns were compared using the weighted pair group method with average linkages.[9] A 95% relatedness cutoff was used to define homologous groups. MRSA isolates were later analyzed for the SCC*mec* cassette and Panton–Valentine leukocidin using previously described techniques.[10,11]

Study

After approval was obtained from the institutional review board of the hospital, a case–control study was initiated in September 2001 and ended in January 2002. A case-patient was defined as an infant who was in the NICU during January 1, 2001, through January 31, 2002, who had a culture positive for MRSA. Case-patients were further divided as MRSA colonized or infected. Prior to October 14, 2001, control-patients were selected randomly from infants who were culture negative for MRSA and stayed in the NICU during the same period as a case-patient. After October 14, 2001, control-patients were randomly selected from infants with negative MRSA surveillance screening cultures. Data were collected for 12 cases of MRSA infection, 6 cases of MRSA colonization, and 68 control-patients in an effort to identify risk factors for and potential sources of the outbreak. Information was entered into an Access database (Microsoft Corp., Redmond, WA) and analyzed using SPSS software (version 10.0; SPSS, Inc., Chicago, IL). Odds ratios (ORs) for risk factors were generated using the chi-square test, and continuous variables were compared using the two-tailed *t* test. Differences were considered significant at a *P* value of .05 or less.

RESULTS

Sporadic cases (0 to 2 per month) of MRSA infection occurred in the NICU during 2001 prior to the outbreak (Fig. 1). Six cases of MRSA infection were reported in the NICU from January to August 2001, representing an attack rate of 5.3%. A cluster of 3 cases of MRSA infection in late September 2001 and 3 other cases of MRSA infection in early October 2001 alerted the staff in the NICU, given an increased attack rate of 21.2% (Fig. 1). The number of MRSA infections per 1,000 patient-days was found

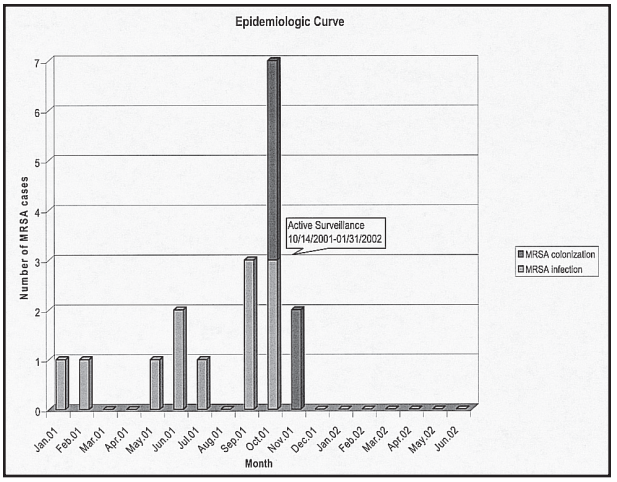

FIGURE 1. Epidemiologic curve showing the monthly number of infants identified with methicillin-resistant *Staphylococcus aureus* (MRSA) infection or colonization in the neonatal intensive care unit from January 2001 through June 2002 and the period of active surveillance. Data on MRSA colonization are shown only for the period of active surveillance.

to be significantly higher for 2001 compared with 2000 (3.97 vs 0.46, respectively; relative risk = 8.59; 95% confidence interval [CI_{95}], 1.99 to 37.00; $P = .0005$).

An active surveillance system to detect unsuspected MRSA colonization was instituted on October 14, 2001, and continued until January 31, 2002. A total of 28 infants were screened; 6 (21.4%) were found to be colonized with MRSA, of whom 4 were identified in October 2001 and 2 in November 2001. All had positive cultures from both the umbilicus and the rectum. Of 110 HCWs screened by nasal swabs, 6 (5.5%) were colonized with MRSA. They included 1 ultrasound technician, 1 respiratory therapist, and 4 registered nurses. Although active surveillance was continued through January 2002, the last case of MRSA colonization among infants was identified on November 17, 2001. Following active surveillance, focused surveillance was continued for MRSA infections and all other infections in the NICU, and no cases of MRSA infection were identified during 2½ years of follow-up (Fig. 1).

Of the 18 case-patients described, 12 were infected and 6 were colonized with MRSA. Among the colonized infants, there were 4 females and 2 males, all of whom were white. There were an equal number of males and females in the infected group, of whom 84% were white and 16% were African American. Most of the control-patients were white (94%) and male (63%). All 12 patients infected with MRSA were identified prior to the initiation of active surveillance on October 14, 2001. All 6 colonized patients were identified by active surveillance, and none developed a subsequent MRSA infection during their stay in the NICU. Five (42%) of the 12 infected patients were infected at more than one site. The sites of isolation of MRSA from infected individuals were distributed as follows: respiratory secretions, 8 of 12 (66%); skin and soft tissue, 5 of 12 (42%); eye infection, 3 of 12 (25%); and blood, 1 of 12 (8%).

Tables 1 and 2 list the significant risk factors for MRSA infection and colonization, respectively. There was an increased risk for MRSA infection among infants who were products of multiple gestation (OR, 5.36; CI_{95}, 1.37 to 20.96), infants with a low mean birth weight (1,347 vs 2,445 g; $P < .001$), and infants with a younger gestational age (28.5 vs 34.4 wk; $P = .0002$). Similar risk factors were present for MRSA colonization. Gavage feeding (OR, 10.33; CI_{95}, 1.28 to 83.37) and endotracheal intubation (OR, 5.97; CI_{95}, 1.22 to 29.31) were associated with an increased risk of MRSA infection but not colonization.

Maternal antibiotic therapy during pregnancy did not increase the rate of subsequent MRSA colonization or infection in newborns. Clinical outcomes were generally favorable. Only one death occurred among patients infected with MRSA, although the death was not directly related to MRSA. However, infants infected with MRSA had a significantly longer stay in the NICU than did infants without MRSA infection (mean, 52 vs 21 days; $P = .003$).

All MRSA isolates from infants and HCWs identified from September 2001 through January 2002 were analyzed by repetitive sequence–based PCR to determine their relatedness. Fourteen of these 18 isolates were homologous at the 95% level, indicating a difference of 1 band or less. Four of the 18 isolates had 90% homology to the remaining isolates and were believed to be subgroups of the same strain (Fig. 2). All 18 MRSA isolates had the type II SCC*mec* cassette and were negative for Panton–Valentine leukocidin, features that are characteristic of hospital-acquired MRSA strains.

DISCUSSION

This MRSA strain had been present in the NICU since at least January 2001 and went unrecognized until a cluster of cases occurred in September 2001. We believe it is crucial to be more aggressive even with a small number of cases of MRSA in NICUs and to initiate appropriate investigations and interventions to prevent nosocomial transmission. A major intervention to deal with this MRSA outbreak included direct observations of the application of infection control measures, including adherence with contact isolation and hand hygiene, with subsequent feedback to improve compliance. Moreover, active surveillance identified additional infants who were colonized with MRSA so that they could also be isolated.

The overall clinical outcome was generally favorable in our patients with MRSA. The 6 infants detected with MRSA colonization after institution of active surveillance did not develop subsequent infections. Of the 12 others who were infected, the rate of severe infections was relatively low, with 1 episode of bacteremia and 3 cases of conjunctivitis. No MRSA-related deaths were reported in our study. Other investigators have shown worse outcomes with higher rates of invasive disease and severe infections and MRSA-related deaths.[4,12,13]

On comparison of case-patients with their corre-

TABLE 1
RISK FACTORS FOR AND OUTCOMES OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTION

	No. (%) of MRSA-Positive Patients	No. (%) of MRSA-Negative Patients	*P**	OR (CI_{95})
Multiple gestation				
Yes	5 (42)	8 (12)		5.36 (1.37–20.96)
No	7 (58)	60 (88)		
Gavage feeding†				
Yes	12 (100)	38 (56)		10.33 (1.28–83.37)
No	0 (0)	30 (44)		
Intubation				
Yes	10 (83)	31 (46)		5.97 (1.22–29.31)
No	2 (17)	37 (54)		
Mean gestational age at birth, wk	28.51	34.41	.0002	
Mean birth weight, g	1,347	2,445	< .001	
Mean length of stay, d	51.83	21.46	.003	

MRSA = methicillin-resistant *S. aureus*; OR = odds ratio; CI_{95} = 95% confidence interval.
*Significant at an alpha level of .05.
†Because all 18 patients with MRSA received gavage feedings, the OR was calculated by adding 1 to each cell.

TABLE 2
RISK FACTORS FOR AND OUTCOMES OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* COLONIZATION

	No. (%) of MRSA-Positive Patients	No. (%) of MRSA-Negative Patients	*P**	OR (CI_{95})
Multiple gestation				
Yes	5 (83)	8 (12)		37.5 (3.9–363.1)
No	1 (17)	60 (88)		
Mean gestational age at birth, wk	29.83	34.41	.0002	
Mean birth weight, g	1,522	2,445	< .001	

MRSA = methicillin-resistant *S. aureus*; OR = odds ratio; CI_{95} = 95% confidence interval.
*Significant at an alpha level of .05.

sponding control-patients, infants with MRSA infection had a significantly increased length of stay, which suggests increased cost. This reinforces previous reports that earlier and successful eradication of outbreaks is cost-effective.[5,6] However, in this study, the length of stay was measured from the time of admission to the time of discharge from the NICU and was not adjusted for birth weight, gestational age at birth, or severity of illness; therefore, it may not be a true reflection of the role of MRSA in prolonging hospital stay.

This study confirmed low birth weight and young gestational age to be significant risk factors for colonization and infection with MRSA. Infants in this NICU who were the product of multiple gestation also had a higher rate of MRSA colonization and infection. This finding has not been consistently described as an independent risk factor in the literature and may be difficult to interpret because these infants often have low birth weights and are born prematurely; moreover, twins in this NICU sometimes shared the same bed, which might have increased the risk of MRSA transmission among them.

Additional risk factors for infection with MRSA in this NICU included gavage feeding and endotracheal intubation. All 12 patients with MRSA infection received gavage feeding and although a statistically significant finding, this may be only a marker of severity of illness or an opportunity for cross-contamination. This study did not specifically address the possibility of intrinsic contamination of the gavage feeding tubes with MRSA as a possible route of transmission, although contamination at the level of the manufacturer seems unlikely. Contamination of the feeding tubes and extrinsic contamination of the feeds may be possible explanations for this finding because gavage feeding requires increased contact between the HCW and the patient and thus provides a greater opportunity for transmission of MRSA. Also, it is unclear whether endotracheal intubation is an independent risk factor for MRSA or an indication of a severe underlying illness that actually

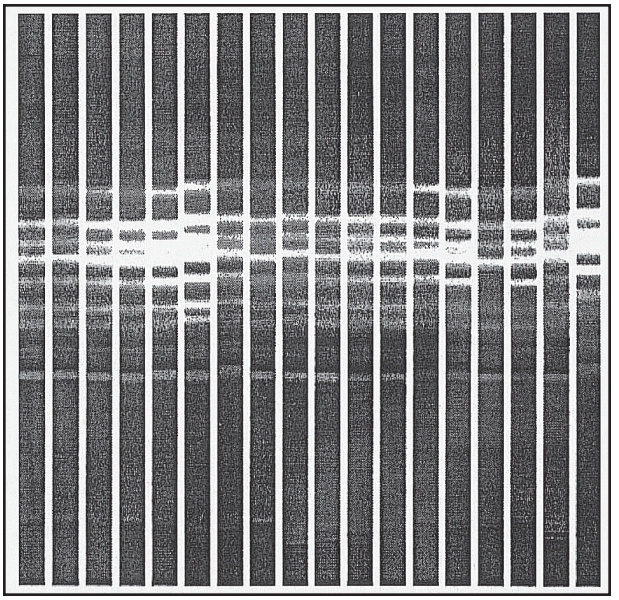

FIGURE 2. Repetitive sequence polymerase chain reaction fingerprints of the 18 methicillin-resistant *Staphylococcus aureus* strains isolated from infants and healthcare workers in the neonatal intensive care unit showing the striking homology among the isolates.

predisposes to MRSA infection. Certain body sites (eg, respiratory tract secretions and the oropharynx), when colonized by MRSA, are particularly resistant to eradication efforts and may explain the increased risk for invasive infections with MRSA in intubated patients.[14]

Decolonization of the HCWs involved the use of intranasal mupirocin in addition to two systemic antibiotics and antibacterial showers. This particular regimen was selected by the local physicians at the study hospital and was not recommended by the authors of this article. In previously described outbreaks, the use of intranasal mupirocin or fuscidic acid as single agents or in combination with hexachlorophene showers or the combination of trimethoprim–sulfamethoxazole and rifampin was enough to decolonize NICU HCWs.[2,4,12] The adoption of an aggressive approach may be warranted in an effort to achieve earlier control of the spread of MRSA in a NICU. However, although the antibiotics were used for a short time and the likelihood of complications and emergence of resistance was low, this regimen should not be recommended for routine use in similar situations.

MRSA strains were compared using the repetitive sequence PCR technique. This technique is performed more easily and more quickly than pulsed-field gel electrophoresis and would therefore be an advantage in outbreak situations. Repetitive sequence PCR using RW3A primer was shown to be at least as discriminatory as and comparable to pulsed-field gel electrophoresis for epidemiologic separation of MRSA strains in two different studies.[15,16] In addition, in the recent article by Healy et al., repetitive sequence PCR was used to type isolates of MRSA recovered from infants in a NICU.[17] This technique is probably going to be used more widely in the future.

This study did not intend to evaluate the effectiveness of each of the infection control methods. Assessing the efficacy of individual measures during an outbreak is a difficult task because hospitals implement multiple control measures simultaneously in an effort to quickly contain the outbreak. Another limitation of the study was difficulty identifying the initial source of MRSA and the exact methods of MRSA transmission, although the MRSA strains from the infants and the HCWs were identical. Because of the structure of the NICU, where the ratio of HCWs to infants was not 1:1, and because of the imperfect documentation of every activity involving the infants, it is difficult to implicate a particular HCW in the spread of MRSA in the NICU.

Successful and durable eradication of a MRSA outbreak was achieved in this NICU after implementing aggressive infection control measures. These measures included direct observation and identification of deficiencies in the application of infection control procedures, education of NICU HCWs about the importance of hand hygiene and proper contact isolation, active surveillance to identify colonized infants and HCWs, establishment of contact isolation and cohorting for infected and colonized patients, and use of decolonization regimens to treat colonized infants and HCWs. We believe that education of HCWs by infection control nurses who ensured compliance with infection control measures played a major role in halting the epidemic and achieving long-term results. Continued education of HCWs is needed to ensure the application of proper contact isolation for patients infected or colonized with MRSA, especially in outbreak situations. Early action, even for a few patients with MRSA, is essential to prevent acquisition and transmission of MRSA in NICUs.

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