MAJOR ARTICLE

Hospital Transmission of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* among Postpartum Women

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Infections caused by community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) are being increasingly observed in patients who lack traditional risk factors. We described 8 postpartum women who developed skin and soft-tissue infections caused by MRSA at a mean time of 23 days (range, 4–73 days) after delivery. Infections included 4 cases of mastitis (3 of which progressed to breast abscess), a postoperative wound infection, cellulitis, and pustulosis. The outbreak strains were compared with the prototype CA-MRSA strain MW2 and found to be indistinguishable by pulsed-field gel electrophoresis. All were *spa* type 131, all contained the staphylococcal chromosomal cassette *mec* type IV, and all expressed Panton-Valentine leukocidin and staphylococcal enterotoxins C and H. The route of transmission was not discovered: the results of surveillance cultures of samples obtained from employees of the hospital, the hospital environment, and newborns were negative for the outbreak strain. We report that MW2, which was previously limited to the midwestern United States, has spread to the northeastern United States and has become a health care–associated pathogen.

For several decades, methicillin-resistant *Staphylococcus aureus* (MRSA) has caused infections in patients with well-described risk factors, including hospitalization, surgery, residence in chronic care facilities, and injection drug use [1]. Recently, MRSA has caused infections in patients lacking traditional risk factors for infection with MRSA [2–7]. Many of these infections have occurred in the community and have affected children and young adults, and some have been associated with substantial morbidity.

Community-acquired MRSA (CA-MRSA) strains have a genotype and a phenotype that are distinct from those of hospital-acquired MRSA. Unlike multidrug-resistant, hospital-acquired strains, for which treatment options are limited, CA-MRSA strains are susceptible to numerous antimicrobial agents, which may include clindamycin, fluoroquinolones, and trimethoprim-sulfamethoxazole [5, 7–9]. Most CA-MRSA strains have caused skin and soft-tissue infections, and the Panton-Valentine leukocidin and staphylococcal enterotoxins have been implicated as possible virulence factors [10–12]. The sequenced prototype CA-MRSA strain MW2 was recovered from a pediatric patient with a case of fatal septicemia in North Dakota in 1998 [3]. MW2 was shown to harbor the *mec* gene on a unique staphylococcal chromosomal cassette (SCC) *mec* type IV [13, 14]. The genetic background of MW2, as defined by multilocus sequence analysis and *spa* typing, was different from that of any of the major MRSA clones isolated globally [15, 16]. Our investigation identified 8 postpartum women who presented to the hospital weeks after delivery with skin and soft-tissue infections

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due to an outbreak strain of MRSA with the same genetic profile as MW2, which suggests that MW2 has become a health care–associated pathogen.

PATIENTS AND METHODS

Identification of cases and case definition. In September 2002, three women presented with cases of postpartum mastitis caused by MRSA that were reported to our Department of Epidemiology at New York–Presbyterian Medical Center (NYPMC; New York) by obstetrical health care professionals. All 3 had delivered healthy, full-term infants in August 2002 at NYPMC, a university-affiliated teaching hospital. On the basis of these cases, we developed a case definition in which postpartum infection was defined as infection with MRSA that was resistant to erythromycin and β-lactam agents but was susceptible to clindamycin, fluoroquinolones, trimethoprim-sulfamethoxazole, gentamicin, rifampin, and tetracycline. The outbreak was reported to the New York State Department of Health by the Department of Epidemiology at this time.

To detect unidentified cases of MRSA in postpartum women and to determine the prevalence of MRSA with the case-defined antibiogram, we reviewed the antimicrobial susceptibility patterns of MRSA strains from all adult and pediatric inpatients and outpatients who were cared for at NYPMC during 2002. We compared the proportion of MRSA strains with the case-defined antibiogram that were recovered from the bloodstream versus those recovered from skin and soft-tissue sites. Prospective surveillance efforts conducted from September 2002 through December 2002 included daily review of readmission diagnoses and clinical microbiology laboratory reports. In addition, meetings were held with the directors of the Departments of Obstetrics, Pediatrics, Neonatology, and Nursing, the clinical microbiology laboratory, and the Pediatric emergency department. A presentation was made to the obstetrical staff about the outbreak, at which time they were told to contact the Department of Epidemiology to report all cases of skin and soft-tissue infections and mastitis in pre- and postpartum women.

Epidemiologic investigations and surveillance cultures. To assess whether MRSA carriage by health care workers was linked to the outbreak, the medical records of case patients, staff assignment lists, and employee interviews were used to identify those workers with possible contact with mothers who had known cases of MRSA infection or their infants. Beginning in September 2002, swab samples of the anterior nares of obstetricians, neonatologists, anesthesiologists, nurses, medical students, and ancillary staff (i.e., obstetrical technologists, nurses' aides, phlebotomists, volunteers, audiologists, and a photographer) were obtained and cultured for MRSA carriage. The culturing effort began on 20 September 2002 and was completed on 8 November 2002; 95% of the staff were cultured by 11 October 2002. No samples were obtained from 2 health care workers who were on extended leaves of absence.

In September 2002, environmental cultures were obtained by swabbing items with a culturette premoistened with sterile 0.9% normal saline. This was an effort to detect a contaminated inanimate reservoir in the labor and delivery area, the postpartum ward, or the well-baby nursery. The surfaces of shared patient care items (e.g., a fetal heart monitor, an infant scale, and a breast pump) were targeted for culturing.

In October 2002, swab samples of the throats and nares of 100 consecutive infants were obtained and cultured immediately before discharge from the well-baby nursery to evaluate infant colonization as a possible source of MRSA acquisition in postpartum women [17]. Samples from other sites were not obtained, because only infant oropharyngeal flora has been implicated in the pathophysiology of postpartum mastitis.

The following assays were used to isolate, identify, and determine the antimicrobial susceptibility of MRSA: oxacillin screening plates containing 6 μg/mL of oxacillin (Mueller-Hinton agar; Becton Dickinson Microbiology Systems), the Staphaurex identification system (Murex Biotech), the MicroScan Walkaway SI (Dade Behring), and the Oxoid penicillin-binding protein latex agglutination test (Oxoid).

Case-control study. A case-control study was performed to identify risk factors for postpartum infections caused by MRSA. A case of postpartum infection was defined as described above. Because all case patients were delivered in August 2002, three control subjects per case patient were randomly selected from a list of patients ($n = 312$) who delivered in August 2002. The list was compiled by the Department of Informatics by means of *International Classification of Diseases, Ninth Revision* codes and diagnosis-related groups. Possible risk factors were assessed by review of the intrapartum medical records of case and control patients. Study groups were compared using χ^2 analysis of demographic and pregnancy-related variables; when expected cell frequencies were <5, Fisher's exact test for categorical variables was used. Student's t test was used to compare the continuous variables of age and length of stay (LOS). Statistical analyses were performed with Excel (Microsoft) and Epi Info 2002 (Centers for Disease Control and Prevention). The institutional review board at NYPMC granted permission to publish this investigation.

Molecular typing studies. Isolates from 7 of the 8 case patients were available for analysis and were genotyped by PFGE with the restriction enzyme *Sma*I, using methods described elsewhere [18]. The PFGE patterns were digitized and analyzed using the GenePath Strain Typing System (Bio-Rad). Strain

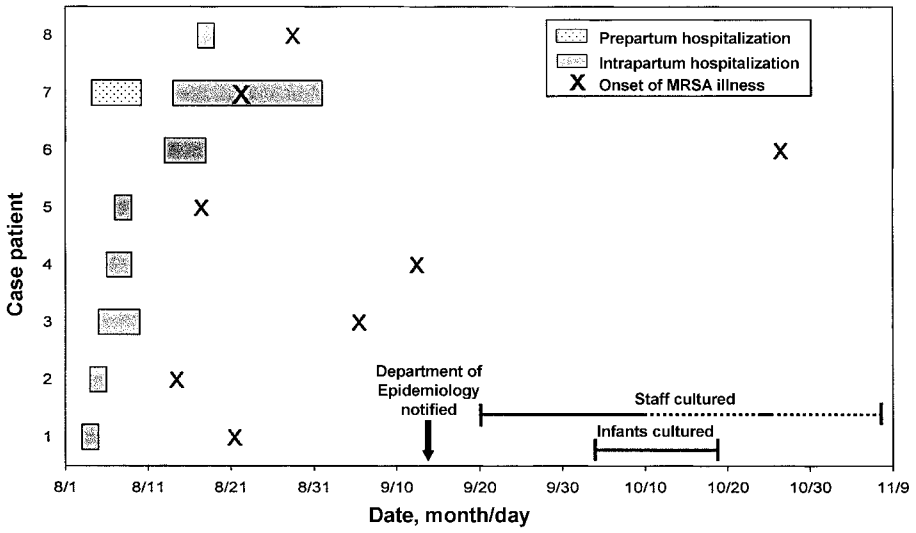

Figure 1. Hospital days and onset of illness among postpartum women with infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) at New York–Presbyterian Medical Center, 2002. The days of prepartum hospitalization on the obstetrical ward (for patient 7) and intrapartum hospitalization (for all case patients) are shown. Markers *(X)* indicate the date of initial onset of skin and soft-tissue infections caused by MRSA. The date when the Department of Epidemiology was notified of the first cases is indicated *(arrow)*. The surveillance efforts for staff and infants are shown. Samples were obtained from the vast majority of staff members and cultured by 10 October; samples obtained from 2 additional staff members were cultured in late October, and a sample obtained from 1 patient was cultured in November.

relatedness was interpreted in accordance with guidelines proposed elsewhere [19].

spa *typing.* Isolates were genotyped by comparative DNA sequencing of the variable number of tandem repeat regions in the *S. aureus* protein A *(spa)* gene. The *spa* typing method and genetic analysis were performed and the nomenclature was specified as described elsewhere [18–20].

SCC* mec *typing. Multiplex PCR analysis to distinguish the 4 genetic elements for SCC *mec* was performed as described elsewhere [21], with the following modification: the *pls* gene was amplified by primers from GenBank accession number AF115379 (PlsF, GGGGTGGTTAATGGTATGAATAAA; PlsR, CGGAATGTTGCTCTTGGTTGTGCGTTTTC), which resulted in a PCR product of 1117 bp.

Detection of leukocidin and enterotoxins. The presence of *pvl* and *seh* was determined by PCR, as described elsewhere [22, 23]. Production of toxic shock syndrome toxin (TSST)–1, staphylococcal enterotoxin B (SEB), and staphylococcal enterotoxin C (SEC) proteins by the strains was evaluated qualitatively by antibody reactivity in a double immunodiffusion assay [24]. After qualitative detection of SEC production was performed, the amount of SEC produced in complex media [25] was determined for all strains. After performance of SDS-PAGE, the band densities of all strains were compared with that of a control. The latter assay allowed comparison of the relative amounts of SEC and staphylococcal enterotoxin H (SEH) made by these strains. The quantity of Panton-Valentine leukocidin produced by the strains was determined using a bioassay [26].

RESULTS

Identification of cases. Eight women were identified—including the initial 3 patients—who developed postpartum infections caused by MRSA with the antimicrobial susceptibility pattern described in the case definition. All 8 case patients delivered their children during the same 2 weeks in August 2002 (figure 1), but the mean time to onset of MRSA infection was 23 days (median, 13.5 days; range, 4–73 days) after delivery. None of the newborn infants delivered by these 8 women were hospitalized in the neonatal intensive care unit (NICU), and none developed infections caused by MRSA during hospitalization or after discharge from the well-baby nursery.

The skin and soft-tissue infections in the 8 case patients included mastitis ($n = 4$), postoperative wound infection after hysterectomy secondary to placenta previa ($n = 1$), cellulitis ($n = 1$), pustulosis ($n = 1$), and urinary tract infection and pustulosis ($n = 1$). Three of the 4 cases of mastitis progressed to breast abscess and required surgical drainage. Five case patients required readmission to 3 different hospitals.

Treatment varied according to the site of infection and the severity of illness. All 8 case patients initially received empirical therapy (e.g., dicloxacillin or cephalexin) for presumed methicillin-susceptible *S. aureus* (MSSA). Samples were obtained for

culture from only 4 case patients before antibiotics were received. After surgical drainage, 1 of the 3 case patients with a breast abscess was successfully treated with trimethoprim-sulfamethoxazole, 1 was treated with ciprofloxacin, and 1 continued to receive cephalexin therapy. The fourth case patient, who had mastitis only, received 2 days of vancomycin therapy followed by 10 days of trimethoprim-sulfamethoxazole treatment. The case patients with postoperative wound infection or cellulitis received vancomycin therapy. The remaining 2 case patients received trimethoprim-sulfamethoxazole for treatment of urinary tract infection and/or pustulosis.

Surveillance efforts. Surveillance efforts failed to reveal the route of transmission of the outbreak strain. None of the 178 employees who had contact with case patients or their newborns had nasal carriage of MRSA, although MSSA was found in 37 (21%). MRSA was not recovered from any of the 13 environmental cultures, but MSSA was recovered from the touch surface of 1 breast pump. None of the 100 infants harbored the outbreak strain, but MSSA was recovered from 4 infants (4%).

Excluding the isolates recovered from the case patients, 77 (4%) of 1861 strains of MRSA isolated at our institution in 2002 had the same antimicrobial susceptibility pattern as the outbreak strain. However, this varied according to site of infection; only 6 (5%) of 120 isolates from the bloodstream had the case-defined antibiogram, compared with 25 (11%) of 223 isolates from skin and soft-tissue sites ($P = .03$, by Fisher's exact test).

Risk factors for acquisition of the outbreak strain. Demographic characteristics and prepartum, intrapartum, and postpartum risk factors were assessed (table 1). None of the 8 case patients had the same postal zip code. The mean age of case patients (31.2 years) and control subjects (32.5 years) was similar ($P = .6$), as was gravidity and parity. All were HIV negative. No patients had been hospitalized on nonobstetrical wards during the year before delivery. Some patients shared the same health care professionals or underwent prenatal diagnostic testing (e.g., ultrasonography and phlebotomy) at the same site, but the care patterns were unique for the 8 case patients. The mean postpartum LOS ($\pm$SD) among case patients and control subjects was comparable (4.8 ± 5.5 vs. 2.6 ± 1.0 days; $P = .3$). Similarly, the median LOS was 2.5 days for both case and control patients (range, 2–18 and 1–5 days, respectively). However, the proportion of case patients (0 of 8) versus control subjects (11 of 24) with group B streptococcal (GBS) vaginal carriage differed ($P = .03$, by Fisher's exact test). The proportion of case and control patients treated with intrapartum antibiotics, including antibiotics with activity against *S. aureus,* was similar, as summarized in table 1.

Results of molecular epidemiologic analysis. The genetic background of the MRSA isolates from 7 of the 8 case patients was determined by PFGE analysis and *spa* typing. The PFGE patterns of the isolates were indistinguishable from that of MW2 (figure 2) and were unique when compared with those of previously typed strains from our institution, including those associated with outbreaks in the NICU [27, 28]. Similarly, DNA sequencing of the protein A repeat region showed that each MRSA isolate had the identical *spa* type 131 (UJJFKBPE) sequence, which matched that of the community-acquired prototype strain, MW2.

Table 1. Demographic data and risk factors in a case-control study of methicillin-resistant *Staphylococcus aureus* infections in postpartum women.

Variable	Case patients ($n = 8$)	Control subjects ($n = 24$)	P
Age, mean years	31.2	32.5	.60[a]
No. of nonobstetrical hospitalizations during the previous year	0	0	…
HIV infection	0	0	…
Group B streptococcal vaginal carriage	0	11 (46)	.03
Gravidity of >1	5 (63)	15 (63)	1.00
Parity of ⩾1	5 (63)	17 (71)	.68
Length of stay, mean days $\pm$ SD	4.8 ± 5.5	2.6 ± 1.0	.30[a]
Caesarian section	3 (38)	5 (21)	.38
Urinary catheterization	7 (88)	13 (54)	.20
Artificial rupture of membranes	2 (25)	11 (46)	.42
Epidural anesthesia	7 (88)	22 (92)	1.00
Vaginal sutures/episiotomy	5 (63)	17 (71)	.68
Intrapartum antibiotic use	1 (13)[b]	10 (42)[c]	.20
Breast-feeding in hospital	3 (38)	12 (50)	1.00

NOTE. Data are no. (%) of individuals, unless otherwise indicated.

[a] By Student's t test.

[b] Clindamycin and metronidazole were administered.

[c] Penicillin was administered to 7 patients, clindamycin was administered to 2 patients, and cefoxitin was administered to 1 patient.

Detection of virulence factors. All strains contained the SCC *mec* type IV and expressed the *pvl, sec,* and *seh* genes. The mean production of SEC and SEH among the strains was 96 μg/mL and 71 μg/mL of culture fluid, respectively. None of the strains expressed staphylococcal enterotoxin A, SEB, or TSST-1.

DISCUSSION

To our knowledge, this is the first published report to document an outbreak of a hospital-acquired and -transmitted CA-MRSA strain. Furthermore, this outbreak is unusual because it caused significant skin and soft-tissue infections, including mastitis with breast abscesses, in postpartum women. We were alerted to the likelihood of hospital acquisition, despite the prolonged latency period, because infections caused by MRSA are rare in this population. We considered CA-MRSA as the causative

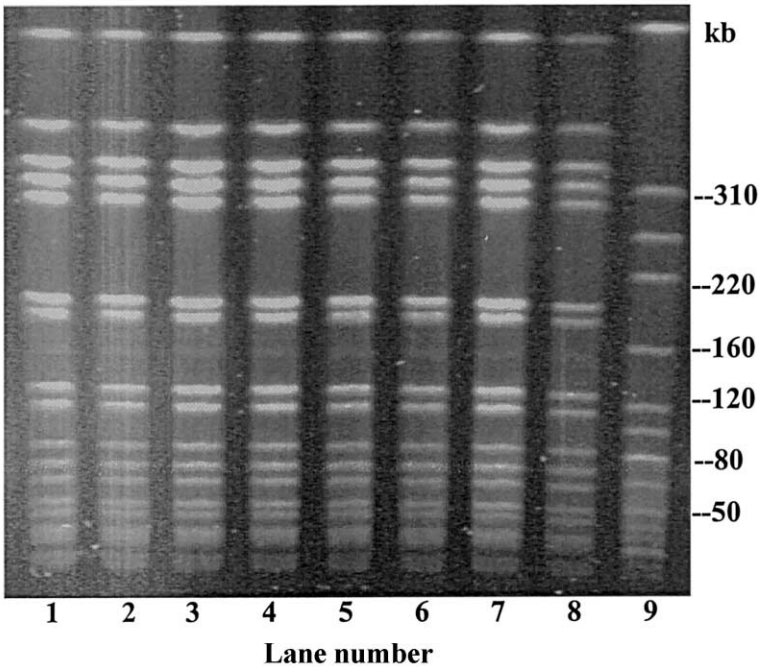

Figure 2. PFGE of strains associated with the outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) in postpartum women at New York–Presbyterian Medical Center, 2002. *Lane 1,* Recovered from a pustule specimen obtained from patient 1. *Lane 2,* Recovered from breast fluid obtained from patient 2. *Lane 3,* Recovered from a breast abscess specimen obtained from patient 3. *Lane 4,* Recovered from a breast abscess specimen obtained from patient 4. *Lane 5,* Recovered from a breast abscess specimen obtained from patient 5. *Lane 6,* Recovered from urine obtained from patient 6. *Lane 7,* Recovered from a surgical wound specimen obtained from patient 7. *Lane 8,* MW2 strain. *Lane 9,* Clone B (associated with a previous MRSA outbreak in the neonatal intensive care unit at New York–Presbyterian Medical Center) [27].

agent because the outbreak strain was unusually susceptible to non–β-lactam antibiotics. This was supported by our review of the antibiotic susceptibility of MRSA strains isolated at our institution in 2002; the case-defined antibiogram occurred in only 4% of isolates.

Postpartum mastitis usually occurs within 6 weeks after delivery [29, 30], with reported rates ranging from 1% to 33% [31]. *S. aureus* is the most common pathogen isolated [30, 32], but mastitis caused by MRSA has rarely been described [33]. Epidemic postpartum mastitis has been linked to outbreaks of MSSA among infants in newborn nurseries [29, 34], whereas sporadic cases of mastitis can be caused by maternal skin or infant oropharyngeal flora [31, 34]. Breast abscess formation can occur in as many as 11% of women with mastitis [29, 30, 32]. The high rate of abscess formation noted in our study may be due to the described virulence factors and/or the delay in effective antibiotic therapy [31].

Our epidemiologic investigations failed to reveal the route of transmission of MRSA during this outbreak. Although both case and control patients spent extensive time in obstetrical health care settings, MRSA was not detected in the employees or environment of such settings. We speculate that patient 7 served as the source of infection for patients 6 and 8 during her postpartum hospitalization. Our efforts to determine the route of transmission may have been thwarted because we were alerted to the outbreak in September 2002, although acquisition had occurred in August 2002. Thus, we hypothesize that the initial source of the outbreak may have been a staff member with transient carriage of the outbreak strain. Alternatively, a case patient or a family member may have been colonized. The only potential risk factor identified in the case-control study was that the GBS vaginal carriage rate was higher among control subjects than it was among case patients. However, the 46% carriage rate noted among control subjects was higher than the usual rate of 20%–30% among patients at NYPMC (A.L.).

Analyses of the genetic background and virulence factors indicated that the outbreak strain was the MW2 strain previously identified [3] and sequenced [14]. This strain of MRSA is unique in its lack of resistance to antimicrobial agents other than β-lactam agents; it contains the *blaZ* gene, which encodes a penicillinase, and the SCC *mec* type IV–encoding penicillin-binding protein 2 [14]. MW2 produces large amounts of SEC and SEH; both of these enterotoxins are involved in toxic shock syndrome [35, 36] and may contribute to the virulence of this strain. In addition, MW2 encodes *bsa,* a putative bacteriocin, and *pvl,* which may be associated with skin and soft-tissue infections due to both MRSA and MSSA strains [37]. Furthermore, MW2 has very few transposons or insertion se-

quences, compared with hospital-acquired clones of MRSA, which results in a more rapid doubling time [14]. It is suggested that the genetic features of MW2 allow this strain to survive in the community and to compete with normal, colonizing flora in healthy hosts. The prevalence of GBS vaginal carriage among control subjects may suggest the production of a bacteriocin and may be a fruitful area of investigation in future studies.

Our investigation had some limitations. As previously noted, we did not demonstrate the route of transmission. Case patients were not assessed for sites of colonization, nor was intrafamilial spread addressed. There may have been undetected cases, given the prolonged latency period, and additional patients with such infections may have presented to other health care facilities. Surveillance cultures to detect colonization of control subjects were not performed, and, as a result, control subjects may have been misclassified. Our analysis of the antimicrobial susceptibility of MRSA strains isolated at our institution did not allow us to compare community- with hospital-based acquisition.

The findings of this investigation have serious public health implications. Our study expands the geographic range of MW2, which was previously limited to the midwestern United States and now has spread to the northeastern United States. Our report suggests that MW2, a community-acquired strain, may become a health care–associated pathogen. This is particularly worrisome, given the short mean LOS among the case patients and the high rate of readmission to several hospitals. Secondary spread of MRSA to vulnerable infants via infected breast milk has already been reported [10], as has intrafamilial transmission of strains of CA-MRSA [38, 39]. Surveys to detect colonization of children with CA-MRSA have been performed, and the rate has varied depending on the population studied. The prevalence of MRSA colonization was low among children visiting emergency departments in New York City (0.2%, 1 of 500 children) [40] and Chicago (2%, 11 of 500 children) [41]. However, colonization rates in day care centers varied from 1.2% (2 of 64 children) to 24% (9 of 40 children) when surveillance cultures were obtained after an index case presented with CA-MRSA infection [42, 43].

The emergence of CA-MRSA has altered health care practices in some communities. Empirical treatment of community-acquired skin and soft-tissue infections with β-lactam agents without culturing specimens obtained from the infected site may not be appropriate, because such infections may be caused by MRSA. Empirical treatment of serious infections with vancomycin while awaiting culture results may be warranted. Active surveillance for CA-MRSA infection and colonization and molecular studies of virulence factors are critical to a complete understanding of the epidemiology of this emerging pathogen, which is becoming an increasingly common constituent of the flora in US communities.

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