MAJOR ARTICLE

Epidemiology and Clonality of Community-Acquired Methicillin-Resistant *Staphylococcus aureus* in Minnesota, 1996–1998

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged among patients in the general population who do not have established risk factors for MRSA. Records from 10 Minnesota health facilities were reviewed to identify cases of MRSA infection that occurred during 1996–1998 and to identify which cases were community acquired. Susceptibility testing and pulsed-field gel electrophoresis (PFGE) subtyping were performed on available isolates. A total of 354 patients (median age, 16 years) with community-acquired MRSA (CAMRSA) infection were identified. Most case patients (299 [84%]) had skin infections, and 103 (29%) were hospitalized. More than 90% of isolates were susceptible to all antimicrobial agents tested, with the exception of β-lactams and erythromycin. Of 334 patients treated with antimicrobial agents, 282 (84%) initially were treated with agents to which their isolates were nonsusceptible. Of 174 Minnesota isolates tested, 150 (86%) belonged to 1 PFGE clonal group. CAMRSA infections were identified throughout Minnesota; although most isolates were genetically related and susceptible to multiple antimicrobials, they were generally nonsusceptible to initial empirical therapy.

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been a common nosocomial pathogen since the 1960s [1–3]. Established risk factors for MRSA infection include recent hospitalization or surgery, residence in a long-term care facility, dialysis, and injection drug use [4–6]. Recently, however, cases of MRSA infection have been reported among patients without established risk factors for MRSA; these infections apparently were community acquired. Community-acquired MRSA (CAMRSA) infections have been reported in Minnesota and North Dakota [7, 8]; Chicago [9–11]; Dallas [12, 13]; and Winnipeg [14] and Toronto, Canada [15]. Although most CAMRSA infections have not been severe, some have resulted in hospitalization and/or death [7]. Despite these reports, little is known about the epidemiology of CAMRSA among patients without established risk factors.

In 1997, the Minnesota Department of Health re-

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ceived, from several Minnesota health care facilities, reports of MRSA infections among young, previously healthy patients. These reports prompted a 3-year survey of 10 Minnesota hospitals to better define the epidemiological and microbiological features of CAMRSA in Minnesota. Hospitals were selected to provide geographic, socioeconomic, and urban/rural diversity. The objectives of the survey were to determine what proportion of *S. aureus* isolates at participating facilities were CAMRSA, to describe the demographic and clinical features of identified cases of CAMRSA infection, and to assess strain relatedness of CAMRSA isolates by pulsed-field gel electrophoresis (PFGE) testing.

METHODS

Hospital enrollment. A convenience sample of 10 hospitals was selected on the basis of location and patient population. The infection control departments of these facilities were contacted; all agreed to participate. Four of the 10 participating hospitals were from the 7-county Minneapolis–St. Paul metropolitan area, and 6 were from greater Minnesota (table 1). The hospitals, which differed in type and size, accounted for ~10% of the licensed hospital beds in Minnesota [16]. The laboratories of participating hospitals served outpatient clinics in addition to their own inpatients and outpatients.

Case ascertainment, case definition, and data analysis. Hospital laboratory databases were reviewed to identify all outpatients and inpatients with MRSA isolates identified from January 1996 through December 1998. We reviewed medical records from the hospitals or, when available, from outlying clinics, and we abstracted information on patient demographics, underlying medical conditions, characteristics of infection, treatment, and MRSA antimicrobial-susceptibility profiles. A "CAMRSA case patient" was defined as any outpatient or inpatient with culture-confirmed MRSA infection who had no history of hospitalization, surgery, renal dialysis, or residence in a long-term care facility within 1 year before the MRSA culture date; no documented history of injection drug use; no permanent indwelling catheter or percutaneous medical device (e.g., tracheostomy tube, gastrostomy tube, or Foley catheter) present at the time of culture; no known MRSA infection before the study; and whose specimen for MRSA culture was obtained within 48 h after admission if the patient was hospitalized. Information was not recorded for patients who did not meet the case definition. Patients who were colonized with MRSA (e.g., family members of MRSA-infected persons who underwent nasal swab sampling to determine whether they were colonized with MRSA) were not considered case patients.

Epidemiological analyses of data were done with Epi Info 6.04c software (Centers for Disease Control and Prevention, Atlanta). The adjusted χ^2 test or 2-tailed Fisher's exact test was

Table 1. Hospital characteristics and number of cases of community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection, by hospital and year, during 1996–1998.

	Hospital characteristics			No. of cases of community-acquired MRSA infection, by year[a]			
Type of hospital, hospital designation (description)	No. of beds	No. of annual *S. aureus* isolates[b]	No. of annual MRSA isolates[b]	1996	1997	1998	Total
Metropolitan hospitals[c]							
A (county/public, urban)	410	979	283	11	16	30	57
B (pediatric, urban)	190	315	103	19	22	13	54
C (private, suburban)	400	1269	168	1	6	11	18
D (private, suburban)	390	545	73	2	1	1	4
Greater Minnesota hospitals							
E (private, community)	90	217	71	18	28	15	61
F (rural, community)	50	158	87	48	47	33	128
G (private, regional)	380	267	17	3	4	7	14
H (private, regional)	90	54	15	6	1	1	8
I (private, community)	140	298	26	2	0	2	4
J (private, community)	180	200	13	2	1	3	6
Total	2320	4302	856	112	126	116	354

[a] Each case represents 1 patient.
[b] Mean number of isolates recovered per year for the period 1996–1998; may include multiple cultures per patient.
[c] From 7-county Minneapolis–St. Paul metropolitan area.

used for comparison of categorical data. Student's *t* test was used for comparison of median values of continuous data.

Isolate characterization. Antimicrobial susceptibility testing was done both at participating hospital laboratories and at the Minnesota Department of Health for confirmation. Results of initial susceptibility testing at hospital laboratories were used when isolates were not available for confirmatory testing at the Minnesota Department of Health. Susceptibility testing at participating hospitals was conducted by broth microdilution with commercial panels. Six laboratories used MicroScan (Dade Behring MicroScan) and 4 used Vitek (bioMérieux). At the Minnesota Department of Health, identification of *S. aureus* was confirmed with a tube coagulase test (Difco Laboratories) [17]. Susceptibility interpretations were made according to break points established by the National Committee for Clinical Laboratory Standards [18]. Oxacillin (methicillin) resistance was confirmed by means of an oxacillin agar screen test (Becton Dickinson) [18]. Disk diffusion was used to test susceptibility to ciprofloxacin, gentamicin, and trimethoprim-sulfamethoxazole [18, 19]. Etest strips (AB Biodisk) were used to test susceptibility to clindamycin, tetracycline, erythromycin, rifampin, and vancomycin.

Molecular subtyping of isolates was done by PFGE with the *Sma*I restriction endonuclease, by means of a published method [20] with the following exceptions: 100 U of mutanolysin was added to lysis solution, and run conditions were 2.2 s for the initial switch time and 37.3 s for the final switch time, with linear ramping for 18 h. Restriction fragment patterns were compared with Molecular Analyst Fingerprinting DST software (Bio-Rad) at a 1% molecular weight sensitivity. Distinct PFGE subtypes were defined by exact matches of all bands in the 30–600-kb range. MRSA isolates were characterized as belonging to a clonal group if they differed from a reference strain by ≤6 bands [21]. PCR testing was done on selected isolates to confirm the presence of the *mec*A gene [22].

RESULTS

CAMRSA case patients: distribution, demographics, and underlying medical conditions. A total of 354 CAMRSA case patients were identified at participating hospitals during the 3-year study (112 case patients in 1996 as well as 126 patients in 1997 and 116 in 1998; table 1). One hundred eighty (51%) of the case patients were female. Of 341 case patients who were Minnesota residents, 132 (39%) lived in the 7-county Minneapolis–St. Paul metropolitan area (53% of the state's total population lived in this area in 1997) [23]. Most case patients were children or young adults (median age, 16 years; range, 1–78 years; figure 1). Excluding the 54 case patients from the pediatric hospital (hospital B), the median age of the case patients was 20 years. A total of 133 (38%) were 1–10 years old;

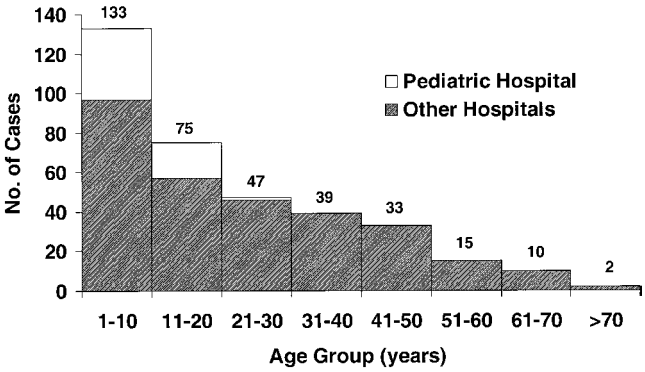

Figure 1. Age distribution of 354 case patients with community-acquired methicillin-resistant *Staphylococcus aureus* who were identified at selected Minnesota hospital laboratories in 1996–1998. Except for 1 pediatric hospital, all participating hospital laboratories served both adult and pediatric patients.

80 (23%) were <6 years old. When hospital F (which predominantly served native Americans) was excluded from analysis, native Americans comprised 91 (40%) of 226 case patients; whites, 47 patients (21%); blacks, 40 (18%); other races, 8 (4%); and those of unknown race, 40 (18%).

The metropolitan hospital laboratories accounted for 133 cases, or 14 cases of CAMRSA infection (range, 2–57 cases) per 1000 *S. aureus* isolates processed per year at these laboratories (table 1). Greater Minnesota hospital laboratories accounted for 221 cases, or 62 cases (range, 4–270 cases) per 1000 *S. aureus* isolates per year. The 5 hospitals with the highest rates of CAMRSA infection (hospitals A, B, E, F, and H) were located in both metropolitan and greater Minnesota (table 1). Compared with case patients from the 5 hospitals with the lowest rates of CAMRSA infection, patients from the 5 hospitals with the highest rates of CAMRSA infection resided in zip-code areas with lower mean annual household incomes ($19,175 vs. $24,728; $P < .001$) [24] and were more predominantly racial minorities (OR, 15.3; 95% CI, 6.9–34.4).

Table 2 presents underlying medical conditions for case patients. Overall, most patients were previously in good health; 268 (76%) had none of the medical conditions listed in the table. The most common conditions were asthma (9%), diabetes (9%), and such dermatologic conditions as eczema or psoriasis (9%). Fifteen case patients (4%) had a household member with a history of MRSA infection.

Clinical characteristics of CAMRSA infections. CAMRSA caused a variety of infections; some patients had >1 type of infection. Of 354 CAMRSA case patients, 299 (84%) had skin infections. Skin infections could be classified as >1 type; 176 (59%) of 299 skin infections were abscesses, 155 (52%) were cellulitis, and 75 (25%) were superficial skin infections, such as impetigo. Thirteen case patients (4%) had otitis (otitis media or otitis externa), 12 (3%) had pneumonia, 12 (3%) had bur-

Table 2. Cases of community-acquired methicillin-resistant *Staphylococcus aureus* identified at selected Minnesota hospitals, by underlying medical conditions and age, in 1996–1998.

Condition	No. (%) of all case patients (n = 354)	No. (%) of case patients aged	
		1–15 years (n = 172)	⩾16 years (n = 182)
Asthma	33 (9)	22 (13)	11 (6)
Diabetes	31 (9)	0	31 (17)
Dermatologic	31 (9)	11 (6)	20 (11)
Psychiatric[a]	11 (3)	3 (2)	8 (4)
Coronary disease	7 (2)	0	7 (4)
Hypertension	4 (1)	0	4 (2)
Cancer	4 (1)	0	4 (2)
Peripheral vascular disease	4 (1)	0	4 (2)
COPD	1 (0.3)	0	1 (1)
None of above	268 (76)	138 (80)	130 (71)

NOTE. Patients may have had >1 underlying condition. COPD, chronic obstructive pulmonary disease.

[a] Does not include substance abuse.

sitis, 11 (3%) had osteomyelitis and/or septic arthritis, 9 (3%) had a bloodstream infection, and 8 (2%) had adenitis. Thirteen patients (4%) had other infections, including upper respiratory tract infections (4), conjunctivitis (3), urinary tract infections (3), endocarditis (1), cholecystitis (1), and psoas abscess (1).

Of 354 CAMRSA patients, 251 (71%) had CAMRSA infection diagnosed and treated while they were outpatients, and 103 (29%) were hospitalized. Forty-one (58%) of 71 patients with nonskin infections were hospitalized, compared with 62 (22%) of 283 patients with skin infections only (OR, 4.9; 95% CI, 2.7–8.8). Twelve (12%) of 103 hospitalized patients required admission to an intensive care unit. Four patients died, including 2 who died of their MRSA infections. One of those who died was a 7-year-old girl with septic arthritis, bacteremia, and respiratory distress syndrome who died of a pulmonary hemorrhage [7]; the other patient was a 36-year-old woman with alcoholism who developed a primary bloodstream infection and multiorgan failure.

Treatment of CAMRSA infections. A total of 340 (96%) of 354 patients were treated with ⩾1 oral or iv antimicrobial agent. Of 334 case patients who received antibiotics and for whom both the antibiotic history and the isolate susceptibilities were known, 282 (84%) initially were treated with antimicrobial agents to which their MRSA isolates were not susceptible, including 277 (83%) who initially were treated exclusively with β-lactam antimicrobials (including cephalosporins), to which all MRSA isolates are uniformly resistant [18]. One hundred seventy-nine case patients (51%) were treated with incision and drainage procedures, and 14 were treated with other surgical procedures (e.g., chest tube drainage or debridement).

Case patients initially treated exclusively with antimicrobials to which their MRSA isolates were not susceptible (inadequate initial therapy) were more likely to be treated with additional antimicrobials at a later date than were patients initially treated with antimicrobials to which their isolates were susceptible (adequate therapy; OR, 2.1; 95% CI, 1.0–4.4). In addition, case patients with inadequate initial therapy were more likely than those receiving adequate initial therapy to be hospitalized ⩾1 day after initiation of treatment (OR, 8.2; 95% CI, 1.3–180.1). Of 17 case patients who developed either pneumonia, bacteremia, or both, 15 (88%) received inadequate initial therapy; 7 of these 15 patients required either hospitalization or surgical treatment at ⩾2 days after initiation of antimicrobial therapy. Of those 7 patients, 4 required intensive care, 3 required artificial ventilation, and 1 died.

Characterization of CAMRSA isolates. Ten isolates that represented different PFGE subtypes were tested for the presence of *mec*A; all results were positive. Oxacillin resistance (used to determine methicillin resistance) was confirmed in all 174 isolates submitted to the Minnesota Department of Health. However, >90% of CAMRSA isolates in this study were susceptible to all other antimicrobial agents tested, with the exception of oxacillin and erythromycin (table 3). All isolates were susceptible to vancomycin.

Of 174 CAMRSA isolates available for PFGE subtyping, 71 (41%) were submitted by 3 metropolitan hospital laboratories, and 103 (59%) were submitted by 3 greater Minnesota hospital laboratories. Among the 174 isolates, 34 distinct PFGE subtypes and 9 PFGE clonal groups were identified. However, 1 PFGE clonal group of subtypes (designated "clonal group A") accounted for 150 (86%) of 174 CAMRSA isolates tested, and 3 subtype patterns within clonal group A accounted for 115 (66%) of all isolates. Clonal group A isolates comprised the majority of the isolates from various age groups (92 [88%] of 105 isolates from case patients 1–15 years old, and 58 [84%] of 69 isolates from those ⩾16 years old), racial groups (103 [91%] of 113 from native Americans, 15 [75%] of 20 from blacks, and 13 [81%] of 16 from whites), and geographic regions (54 [76%] of 71 from metropolitan hospitals, and 96 [93%] of 103 from greater Minnesota hospitals).

Hospital B, the pediatric hospital, had saved all MRSA isolates obtained during 1996–1998. Therefore, we were able to obtain MRSA isolates from MRSA-infected patients who did not meet the case definition for CAMRSA infection (and who therefore had nosocomial infection) at that hospital. CAMRSA infections were more frequently caused by clonal group A organisms than were nosocomial MRSA infections. During 1996–1998, 49 (73%) of 67 patients with CAMRSA infections had isolates from clonal group A, compared with only 8 (17%) of 47 patients with nosocomial MRSA infections (OR, 13.3; 95% CI, 4.8–38.0). Furthermore, compared with nosocomial

Table 3. Community-acquired methicillin-resistant *Staphylococcus aureus* isolates identified at selected Minnesota hospitals by antimicrobial susceptibility status, 1996–1998.

Antibiotic	No. of isolates tested[a]	No. (%) of isolates that were		
		Susceptible	Intermediately susceptible	Resistant
Oxacillin	354	0	0	354 (100)
Erythromycin	318	203 (64)	29 (9)	86 (27)
Clindamycin	348	325 (93)	3 (1)	20 (6)
Ciprofloxacin	325	303 (93)	11 (3)	11 (3)
Tetracycline	249	236 (95)	1 (0.4)	12 (5)
TMP-SMZ	342	333 (97)	0	9 (3)
Gentamicin	247	240 (97)	2 (1)	5 (2)
Rifampin	211	209 (99)	2 (1)	0
Vancomycin	343	343 (100)	0	0

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Some isolates were tested at participating hospital laboratory only.

MRSA isolates, CAMRSA isolates were more likely to be susceptible to all 5 of the following antimicrobials: trimethoprim-sulfamethoxazole, clindamycin, ciprofloxacin, gentamicin, and tetracycline (OR, 30.2; 95% CI, 9.0–134.7).

DISCUSSION

This investigation established that CAMRSA infections (defined as MRSA infections in patients without established risk factors for MRSA) occurred in both rural and urban areas of Minnesota, predominantly among children and young adults. This is the first study of CAMRSA conducted in multiple locations that assessed both adult and pediatric populations. This study was initiated because cases of CAMRSA infection were noted in several regions of Minnesota. Rather than establish statewide population-based surveillance for CAMRSA infection, we elected to first survey a sample of health care facilities in the state to better define the problem. Systematic assessment cases of CAMRSA infection at the 10 participating facilities demonstrated marked variability in rates of CAMRSA by hospital. This variability may be due to differences in patient populations served but could not be adequately assessed in this study.

The clonality of the CAMRSA isolates by PFGE was striking and supports our conclusion that MRSA infections in this study truly were community acquired. More than 80% of CAMRSA isolates from Minnesota were clonally related by PFGE (clonal group A). In fact, although the Minnesota Department of Health has identified >250 different MRSA PFGE subtypes since 1995, just 3 closely related subtype patterns accounted for two-thirds of all CAMRSA isolates tested. CAMRSA isolates with clonal group A PFGE patterns were also responsible for most infections in published reports from other Midwestern locations. Investigators from the University of Illinois in Chicago, who have published reports on CAMRSA [9, 25], sent community-acquired and nosocomial MRSA strains to the Minnesota Department of Health in a blinded fashion. The CAMRSA strains from Chicago were clonal group A organisms, and the most common CAMRSA PFGE subtype pattern identified in Chicago [26] also was the most common subtype pattern identified in Minnesota. Furthermore, CAMRSA isolates from 2 North Dakota pediatric patients who died in 1998 and 1999 belonged to PFGE clonal group A [7].

The CAMRSA clonal group A strains described in this report were unrelated, as determined by PFGE, to common nosocomial MRSA strains obtained from hospital B in Minnesota. Furthermore, PFGE subtyping at the Centers for Disease Control and Prevention (Atlanta) demonstrated that the CAMRSA clonal group A strains discussed in this report are unrelated to common nosocomial MRSA strains in New York [27], vancomycin-intermediate MRSA isolates from the United States and Japan [28, 29], Canadian epidemic nosocomial MRSA strains, and European epidemic nosocomial clones (EMRSA-1 through EMRSA-16) [30–32]. The antimicrobial resistance patterns for CAMRSA isolates identified in this study also support the hypothesis that these isolates are distinct from nosocomial strains, although this needs to be confirmed in a future study. CAMRSA isolates in this study were generally susceptible to antimicrobials other than β-lactams, whereas most nosocomial MRSA isolates are resistant to antimicrobials other than β-lactams [4, 27, 33–37].

The emergence of MRSA among healthy young persons in the general population has important clinical consequences, because CAMRSA isolates are nonsusceptible to β-lactam antibiotics, which are often used as empirical therapy for a variety of infections. In this study, for example, 83% of patients were initially treated exclusively with β-lactams. Inadequate empir-

ical antimicrobial therapy could allow MRSA infections to progress, leading to clinical complications [7, 8].

To prevent clinical complications associated with CAMRSA infections, health care providers should consider practice modifications in areas where such infections are prevalent. These modifications might include more aggressive culturing of infected sites and evaluation of the empirical use of β-lactam antimicrobials, particularly for the treatment of infections with a high likelihood of being staphylococcal in origin. Because most CAMRSA isolates were susceptible to multiple antimicrobial classes (including trimethoprim-sulfamethoxazole, tetracyclines, quinolones, and clindamycin), treatment of CAMRSA infections should not routinely require the use of vancomycin.

This study has several limitations. First, the data collected were not population based; therefore, our sample of hospitals is not necessarily representative of hospitals in the entire state. Second, it is possible that some cases of nosocomial MRSA were misclassified as CAMRSA. Although medical records were carefully reviewed to ascertain hospitalizations that occurred during the past year, medical records were not always complete and case patients were not interviewed. Therefore, some health care–associated exclusion criteria may have been missed. Additional population-based surveillance studies and/or case-control studies with interviews of case patients and controls are needed to address these issues.

CAMRSA poses important challenges for public health officials. Surveillance data are needed to determine the geographic distribution of cases and to monitor the emergence of this important problem in the community. Also, local information is needed to direct clinical decisions about treatment. However, public health resources for establishing new surveillance systems are limited. Creative approaches to surveillance, such as tracking infections from sentinel hospitals in areas that serve high-risk communities or performing periodic cross-sectional surveys, should be considered. The Centers for Disease Control and Prevention and other federal agencies recently released a document entitled "Public Health Action Plan to Combat Antimicrobial Resistance" [38]. In the document, development of a national antimicrobial resistance surveillance plan is identified as a top-priority item for action at the federal level. We concur with the need for a national antibiotic resistance surveillance plan and believe that it is essential that the plan address such emerging issues as CAMRSA.

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