Community-Acquired Methicillin-Resistant Staphylococcus aureus in a Rural American Indian Community

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Methicillin-resistant Staphylococcus aureus (MRSA) first emerged as a nosocomial pathogen in the early 1960s. Since then, data from the Centers for Disease Control and Prevention’s National Nosocomial Infection Surveillance system indicate that the occurrence of MRSA infection in US hospitals has been increasing steadily and that MRSA accounted for more than 40% of S aureus isolates in 1998. Established risk factors for MRSA infection include recent hospitalization, recent surgery, residence in a long-term care facility, and injection drug use.

Methicillin-resistant strains of S aureus are resistant to all β-lactam antibiotics and, frequently, to many other antibiotic classes. β-Lactam resistance is due to an alteration of the penicillin-binding protein PBP 2a, which is encoded by the chromosomal gene mecA. Most circulating strains of MRSA appear to be derived from only 2 or 3 clones. Once introduced into a microbial population, mecA may be transferred horizontally and recombined among methicillin-susceptible S aureus (MSSA) cells. This has led to the global spread of MRSA in association with increasing geographic mobility of infected patients and carriers of the organism.

Despite the increased incidence of MRSA infection in nosocomial settings, reports of infection acquired in the community have been relatively rare. Four recent deaths due to MRSA infection in previously healthy children in the Midwest suggest that serious MRSA infections can be acquired in the community in rural as well as urban locations.

Objectives To document the occurrence of community-acquired MRSA infections and evaluate risk factors for community-acquired MRSA infection compared with methicillin-susceptible S aureus (MSSA) infection.

Design Retrospective cohort study with medical record review.

Setting Indian Health Service facility in a rural midwestern American Indian community.

Patients Patients whose medical records indicated laboratory-confirmed S aureus infection diagnosed during 1997.

Main Outcome Measures Proportion of MRSA infections classified as community acquired based on standardized criteria; risk factors for community-acquired MRSA infection compared with those for community-acquired MSSA infection; and relatedness of MRSA strains, determined by pulsed-field gel electrophoresis (PFGE).

Results Of 112 S aureus isolates, 62 (55%) were MRSA and 50 (45%) were MSSA. Forty-six (74%) of the 62 MRSA infections were classified as community acquired. Risk factors for community-acquired MRSA infections were not significantly different from those for community-acquired MSSA. Pulsed-field gel electrophoresis subtyping indicated that 34 (89%) of 38 community-acquired MRSA isolates were clonally related and distinct from nosocomial MRSA isolates found in the region.

Conclusions Community-acquired MRSA may have replaced community-acquired MSSA as the dominant strain in this community. Antimicrobial susceptibility patterns and PFGE subtyping support the finding that MRSA is circulating beyond nosocomial settings in this and possibly other rural US communities.

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until recently. In the 1990s, studies of MRSA in Western Australia,11,12 the Canadian prairies,13 Illinois,14,15 southern Texas,16 Hawaii,17 and California18 suggested the emergence of MRSA as a community-acquired pathogen. Medical record reviews documented that most patients had no established risk factor for MRSA infection.3,11,14-18 Furthermore, antimicrobial susceptibility patterns showed that, unlike many nosocomial strains of MRSA, community-acquired MRSA isolates tended to remain susceptible to most non-β-lactam antibiotics.3,11,12,14,15,17,18 All studies from the United States and Canada, however, were conducted in large hospitals in urban areas, where patients are more likely to have exposure to tertiary care facilities.3,13-18 The only studies that examined community-acquired MRSA among patients from nonurban areas were those conducted in Australia.11,12 A 1996 national survey of Indian Health Service (IHS) facilities, many of which provide few or no inpatient services, found that, overall, 40% (600/1490) of S aureus isolates tested from the Midwest and Northern Plains were MRSA (IHS, unpublished data, 1996). Subsequently in 1999, 4 deaths among children in Minnesota and North Dakota, 1 of which occurred in an American Indian, were attributed to community-acquired MRSA infection.19 These findings suggested that MRSA was being acquired outside nosocomial settings. We therefore sought to examine the prevalence of community-acquired MRSA and to evaluate risk factors for community-acquired MRSA infection compared with those for community-acquired MSSA infection in a rural American Indian community.

METHODS
The study was conducted at a small IHS hospital with a busy outpatient clinic located in a rural midwestern community. The annual catchment population was 8311. All laboratory-confirmed S aureus infections among patients treated at this facility between January 1 and December 31, 1997, were evaluated using a retrospective cohort study design and medical record review. Cases of laboratory-confirmed MRSA infection were compared with those of laboratory-confirmed MSSA infection. The research proposal for this study was approved by the IHS National Institutional Review Board and the local tribal council.

Laboratory Methods
Initial antimicrobial susceptibilities were determined locally using MicroScan panels (Dade Behring MicroScan Inc, West Sacramento, Calif). Confirmatory antimicrobial susceptibility testing of 50 MRSA isolates (81%) was conducted at the Minnesota Department of Health using Etest (AB Biodisk, Solna, Sweden).20-22 Oxacillin agar screen testing and pulsed-field gel electrophoresis (PFGE)23-25 were performed on a sample of MRSA isolates. Pulsed-field gel electrophoresis was performed using a previously published method26 with slight modifications (100 U of mutanolysin were added to the lysis solution; run conditions were 2.2 seconds for the initial switch time and 37.3 seconds for the final switch time, with linear ramping for 18 hours; and SeaKem Gold agarose [BioWhittaker Molecular Applications, Rockland, Me] was used in place of PFGE-certified agarose). The control strain, NCTC 8325, was run 3 times on a 10-well gel and 4 times on a 15-well gel. Restriction-fragment patterns derived using the enzyme SmaI (Promega, Madison, Wis) were compared using Molecular Analyst Fingerprinting Data Sharing Tools, version 1.6 (Bio-Rad, Hercules, Calif) set to a 1% molecular weight position tolerance. Pulsed-field gel electrophoresis types were defined as having indistinguishable band patterns in the 30- to 600-kilobase range and were considered clonally related when patterns differed from a reference strain by 3 or fewer bands.27 Five MRSA isolates representing different PFGE subtypes underwent polymerase chain reaction amplification for detection of the mecA gene.28

Data Collection
Laboratory records from the on-site laboratory for 1989-1997 were reviewed. We gathered information from patients’ medical records using a standardized data abstraction instrument. Abstracted data included basic demographic information, anatomical site of infection, clinical symptoms, and treatment of S aureus infection. Information on exposure to established risk factors for MRSA infection in the year before infection was also obtained. No patients were contacted directly.

Infections were classified as community acquired if isolates were obtained in an outpatient setting or less than 48 hours after hospital admission and if patients had no history of hospitalization, renal dialysis, or residence in a long-term care facility during the year before infection and no documented history of injection drug use. Risk factor analyses were limited to cohort members who met the criteria for a community-acquired infection.

Statistical Analysis
Adjusted χ² or 2-tailed Fisher exact tests were performed for comparisons of categorical data using Epi Info, version 6.04c,29 and StatXact 3.30 Risk ratios (RRs) and exact 95% confidence intervals (CIs) were also calculated for all categorical data in evaluating exposures among cohort members. Kruskal-Wallis tests were used to evaluate non-normally distributed continuous data.

RESULTS
Demographics
From 1989 to 1997, MRSA infections increased dramatically in this community (Figure 1). Our cohort contained 112 patients with S aureus infections during 1997, of whom 62 (55%) had an MRSA infection and 50 (45%) had an MSSA infection. All study patients were American Indians. Infections occurred year-round, and there were no significant differences between patients with MRSA and patients with MSSA with regard to sex or age (median age for MRSA patients,
Community-Acquired vs Non-Community-Acquired Infections

Most MRSA infections (46 [74%]) were classified as community acquired. A similar proportion of MSSA infections (32 [64%]) could also be classified as community acquired.

Antimicrobial susceptibility patterns of MRSA isolates demonstrated uniform resistance to β-lactam antibiotics. Most community-acquired MRSA isolates, however, were susceptible to many other non-β-lactam antibiotics (TABLE). Community-acquired MRSA isolates were significantly more likely than non–community-acquired MRSA isolates to be susceptible to ciprofloxacin (P = .01), although other differences were not significant. All 5 tested MRSA isolates demonstrated presence of the mecA gene.

Fifty (81%) of 62 MRSA isolates were available for PFGE subtyping. Thirty-eight isolates (76%) were from community-acquired MRSA infections and 12 isolates (24%) were from non–community-acquired infections. One clonal group, designated as group A, accounted for 80% of all isolates tested. Group A subtypes were significantly more likely among community-acquired isolates (34/38 [89%]) than non–community-acquired isolates (6/12 [50%]) (P = .007). The 3 most commonly identified PFGE group A subtype patterns, which accounted for 32 of the 34 community-acquired group A isolates, were distinct from non–group A subtypes from residents of a long-term care facility in the community (FIGURE 2).

Among community-acquired infections, a similar proportion of patients with community-acquired MRSA (89%) and community-acquired MSSA (94%) presented with skin infection (P = .76). Six patients with community-acquired MRSA (13%) and 1 patient with community-acquired MSSA (3%) were hospitalized because of their infection (P = .31). No deaths were attributed to S aureus infection in either group.

Prior Health Care Exposures and Underlying Medical Conditions

Among patients treated at either the outpatient clinic or the emergency department during the year before their infection, 45 (60%) of 75 developed a community-acquired MRSA infection compared with 1 (33%) of 3 patients who were not treated at the clinic/ emergency department (RR, 1.80; 95% CI, 0.56-59.76). The median of 7 clinic/ emergency department visits (range, 1-22 visits) among patients with community-acquired MRSA was not significantly different from the median of 6 visits (range, 1-34 visits) among patients with community-acquired MSSA (P = .19). Among patients with underlying chronic health conditions, 12 (50%) of 24 developed a community-acquired MRSA infection compared with 34 (63%) of 54 patients with no underlying chronic condition (RR, 0.79; 95% CI, 0.34-1.36).

In regard to exposure to antibiotics, we found no significant difference between patients with community-acquired MRSA and community-acquired MSSA. Among patients prescribed at least 1 course of antibiotics during the year before infection, 31 (61%) of 51 developed community-acquired MRSA compared with 15 (56%) of 27 who were not prescribed antibiotics (RR, 1.09; 95% CI, 0.65-2.11). Of those who received an antibiotic course, the median number of antibiotic courses for patients with community-acquired MRSA was 3.0 vs 2.0 for those with community-acquired MSSA; the difference was not significant (P = .32).

COMMENT

The proportion of MRSA isolates in this community increased substantially from 1989 to 1997, suggesting that community-acquired MRSA has emerged only recently. Low socioeconomic status,
Evidence supporting community acquisition is found in the PFGE patterns of these community-acquired MRSA isolates, which were distinct from the PFGE patterns of circulating nosocomial MRSA strains. Subtyping by PFGE revealed that most community-acquired MRSA infections were caused by clonally related MRSA subtypes that were either indistinguishable from or clonally related to the community-acquired MRSA subtypes associated with the previously reported pediatric fatalities in the Midwest. We found no epidemiologic links between patients in this community and any of the 4 fatal cases of community-acquired MRSA. The lack of any connections other than geographic proximity in the Midwest suggests that community-acquired MRSA may be emerging throughout this region and that this American Indian community can be regarded as a sentinel for emerging community-acquired MRSA.

Community-acquired MRSA may be replacing community-acquired MSSA in our study community. Although we would expect exposure to established risk factors for MRSA to have resulted in more MRSA infections than MSSA infections, this did not occur. Because there is apparently no significant evolutionary “cost” in fitness for strains of MRSA relative to MSSA, even slight selective pressure from antimicrobial drug use may cause MRSA to outtake MSSA strains in a microbial population. This has been a common pattern for the establishment of MRSA in nosocomial settings. A similar pattern may be observed in community settings.

Misclassification bias is a potential limitation of this study. Our stringent definition of community-acquired infection could have caused us to underestimate the true proportion of these infections. In addition, undocumented nosocomial exposures and antibiotic use could have occurred, such as when study participants sought health care at other facilities. Because the IHS is essentially a form of managed care, however, care received outside the system is usually documented, decreasing the likelihood that there were unidentified nosocomial exposures. Finally, patients with MRSA could have had a close contact who was exposed to a nosocomial setting, thereby providing an indirect nosocomial source of infection.

Based on our findings, health care practitioners in rural communities in the Midwest should consider the possibility of MRSA infection among young, healthy patients without a history of nosocomial exposure. Culturing suspected Staphylococcus aureus infections and conducting antibiotic susceptibility testing, particularly in communities with known high rates of MRSA infection, is important to ensure that appropriate antibiotic therapy is provided. The report describing 4 deaths in previously healthy young persons in the Midwest highlights the potentially deadly consequences of community-acquired MRSA infection. Fortunately, most community-acquired MRSA isolates in this study were susceptible to a variety of antimicrobial agents in addition to vancomycin. Health care practitioners should be particularly attentive to judicious use of antibiotics in outpatient settings to avoid an expanding spectrum of antibiotic resistance among strains of community-acquired MRSA.

Socioeconomic factors that may have facilitated our recognition of the emergence of community-acquired MRSA in this rural community are not unique to American Indian populations, and it is likely that MRSA is becoming preva-
MRSA is growing and that even rural communities are not sheltered.

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