Methicillin-resistant *Staphylococcus aureus* (MRSA) infections and methamphetamine use are emerging public health problems. We conducted a case–control investigation to determine risk factors for MRSA skin and soft tissue infections (SSTIs) in residents of a largely rural southeastern community in the United States. Case-patients were persons >12 years old who had culturable SSTIs; controls had no SSTIs. Of 119 SSTIs identified, 81 (68.1%) were caused by MRSA. Methamphetamine use was reported in 9.9% of case-patients and 1.8% of controls. After we adjusted for age, sex, and race, patients with MRSA SSTIs were more likely than controls to have recently used methamphetamine (odds ratio 5.10, 95% confidence interval 1.55–16.79). MRSA caused most SSTIs in this population. Transmission of MRSA may be occurring among methamphetamine users in this community.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a growing public health problem for urban and rural communities in the United States. Skin and soft tissue are the most common sites of MRSA infection, comprising >75% of MRSA disease. Skin and soft tissue infections (SSTIs), commonly caused by *S. aureus*, are frequently associated with injection drug use, particularly in injection drug users in urban Detroit during the early 1980s. Illegal methamphetamine use in the United States led to a rising number of methamphetamine-related hospital admissions from the early 1980s through the early 2000s. In 2004, 0.2% of the national population ≥12 years of age reported using methamphetamine in the previous month; 0.6% reported using it in the previous year. The prevalence of methamphetamine use has been reported to be >5% in at-risk populations such as young men from low-income, urban neighborhoods and urban HIV-positive men who have sex with men.

On August 2, 2005, the Georgia Division of Public Health invited the Centers for Disease Control and Prevention (CDC) to assist in an on-site investigation of increased SSTIs among patients of a low-cost, fee-for-service clinic in rural Georgia. The clinic’s nurse practitioner had noted a history of methamphetamine use in multiple patients with SSTIs. Methamphetamine use has been associated with MRSA skin infections among urban HIV-positive men who have sex with men, but no study has evaluated the association of methamphetamine use and MRSA infection in a community with a large rural population. The objectives of this investigation were to define the public health effects and to determine risk factors, including methamphetamine use, for MRSA SSTI among residents of a community in the southeastern United States.

**Methods**

**Epidemiologic Investigation**

We conducted a prospectively enrolled case–control investigation at 3 emergency departments and 3 urgent care clinics in Georgia from September 6 through October 31, 2005. Two low-cost urgent care clinics that serve primarily
low-income populations and all emergency departments in
a 3-county area were included in an attempt to capture sites
where methamphetamine users might seek medical care for
SSTI. The third urgent care clinic was affiliated with one of
the participating hospitals but was located in a neighboring
county. According to the 2000 US Census, 43.9% of the
population of these 3 counties lives in rural areas (13).

We defined a case-patient as a person >12 years of age
with a laboratory culture–confirmed SSTI who came to a
participating emergency department or clinic for treatment
during the investigation period. Clinicians at participating
institutions identified patients with culturable SSTIs and
were asked to incise, drain, and culture all infected skin
and soft tissue. Patients with SSTIs that were not culturable,
such as simple cellulitis, were not included. Patients
whose primary language was not English were enrolled if
they could speak English fluently enough to answer survey
questions. Patients with new or recurrent SSTI could also
be enrolled; however, we excluded patients who had previ-
ously enrolled in the investigation.

Controls were patients >12 years of age with no current
skin infection who were frequency matched by investiga-
tion site at a rate of 3 controls to 1 case-patient with MRSA
infection. Controls were excluded if they reported a current
skin infection or if infection was identified on physical ex-
amination. Persons could be enrolled as control patients if
illness was minor and comparable in severity to an SSTI.
For example, patients with major trauma and critically ill
patients were excluded from control selection.

Upon seeking treatment, patients voluntarily consent-
ed to be interviewed by trained staff of the participating
healthcare facilities, local public health departments, or
CDC to identify SSTI case-patients. To ensure as much
privacy as possible, the interviews were usually conducted
in the patient’s room with no family or friends present. The
interview survey contained questions about demographics,
clinical history, and potential risk factors for SSTI. Each
patient was asked a specific question about methamphet-
amine use: “In the past 3 months, have you used metham-
phetamine (crystal meth or meth)?” If the patient answered
yes, 2 follow-up questions were asked: 1) “How did you
take methamphetamine?” with the choices “smoked or
inhaled,” “injected,” or “swallowed or took pills,” and 2)
“Have you shared drug equipment or rinse water with any-
one else, including a significant other?” To identify health-
care exposure, patients were asked whether they had had
surgery or dialysis or if they had stayed overnight in a hos-
pital within the previous 3 months. All patients, and their
parents if the patients were <18 years of age, were given a
letter explaining the investigation and asked to give verbal
informed consent to enroll in the investigation.

We examined trends in S. aureus skin infections and
cultures at one of the main emergency departments in our
investigation by reviewing billing codes and laboratory mi-
crobiology reports from January 2004 through September
2005, the start of the case–control survey investigation.
This investigation was deemed exempt from review by the
CDC Institutional Review Board because it was part of a
public health response by CDC and the Georgia Division of
Public Health.

Laboratory Investigation

Specimens were obtained from at least 1 infection
site in all case-patients. Staff at all 3 hospital emergency
departments and the urgent care clinic affiliated with 1
of the hospitals collected cultures and performed antimicro-
bial drug susceptibility testing at their facility. Two
low-cost, urgent care clinics sent all cultures to CDC for
culture and antimicrobial drug susceptibility testing. All 6
investigation sites sent both MRSA and methicillin-sus-
ceptible S. aureus (MSSA) isolates to CDC for further
characterization.

All available isolates from methamphetamine users and
a random sample of isolates not related to methamphetamine
use from each of the 6 investigation sites were tested at CDC
for antimicrobial susceptibility by the Clinical and Labora-
try Standards Institute broth microdilution method (14). We
tested for susceptibility to chloramphenicol, clindamycin,
daptomycin, doxycycline, erythromycin, gentamicin, levo-
flaxacin, linezolid, oxacillin, penicillin, rifampin, tetracy-
cline, trimethoprim-sulfamethoxazole, and vancomycin. In
addition, we performed the cefoxitin disk diffusion test to
predict mecA-mediated resistance to oxacillin (14) and the
D-zone test for inducible clindamycin resistance (15). Iso-
lates were also tested by using PCR for genes encoding the
staphylococcal cassette chromosome mec (SCCMec) resist-
tance complex, Panton-Valentine leukocidin (PVL) cytotox-
in, and toxic shock syndrome toxin (16). Chromosomal DNA
was analyzed by pulsed-field gel electrophoresis (PFGE) af-
after digestion with SmaI restriction endonuclease (17). The
relatedness of PFGE patterns in different isolates was defined
by using Dice coefficients and 80% relatedness by the un-
weighted pair-group method with arithmetic averages (Ap-
plied Maths, BioNumerics, Austin, TX, USA) (18).

Statistical Methods

We conducted univariate analysis of the data to de-
scribe patient demographics and compared binary and
categorical variables with the χ2 test; continuous variables
were compared by using the t test with unequal variances.
We evaluated risk factors for MRSA SSTIs by using condi-
tional logistic regression with stratification by investigation
site. Risk estimates were adjusted for age (categorized as
<18 years, 19–34 years, 35–64 years, and ≥65 years), sex,
and race (categorized as white and nonwhite) because they
were potential confounding variables.
Results

Epidemiologic Investigation

We identified 119 case-patients with skin infections in the investigation. MRSA was isolated from 81 (68.1%) of the skin and soft tissue cultures, MSSA from 20 (16.8%), and bacteria other than \textit{S. aureus} from 18 (15.1%) (Table 1). Compared with controls with no skin infection, a higher percentage of patients with MRSA SSTIs were male (p<0.001). The proportion of patients that were male did not differ significantly between controls and patients with either MSSA or non–\textit{S. aureus} SSTIs (p = 0.67 for MSSA, p = 0.12 for non–\textit{S. aureus}) or between patients with MRSA and MSSA SSTIs (p = 0.16).

Fifteen patients who reported recently using methamphetamine were identified: 8 with MRSA SSTIs, 2 with MSSA SSTIs, and 5 controls. Half (8 [53.3%]) of the methamphetamine users were male. Ten percent of patients with MRSA skin infections (8/81) reported using methamphetamine. Ten percent of patients with MSSA SSTIs, and 5 controls. Half (8 [53.3%]) of the methamphetamine users were male. Ten percent of patients with MRSA SSTIs were male (p<0.001). The proportion of patients that were male did not differ significantly between controls and patients with either MSSA or non–\textit{S. aureus} SSTIs (p = 0.12 for non–\textit{S. aureus} SSTIs (p = 0.67 for MSSA, p = 0.12 for non–\textit{S. aureus}) or between patients with MRSA and MSSA SSTIs (p = 0.16).

Methamphetamine use in the past 3 months, significantly more than the 2% of controls (5/283) who reported this behavior (p<0.001).

After adjusting for age, sex, and race, we determined that patients with MRSA SSTI were significantly more likely to have recently used methamphetamine than were controls (adjusted odds ratio [AOR] 5.10, 95% confidence interval [CI] 1.55–16.79) (Table 2). Of the 8 methamphetamine users with MRSA SSTIs, most (5 [62.5%]) smoked or inhaled the drug. Only 1 (12.5%) injected the drug, and 1 (12.5%) took the drug orally. Of 1 methamphetamine user with MRSA SSTI, we could not determine the route of drug administration. Of the 8 methamphetamine users with MRSA SSTIs in our investigation, 2 (25.0%) reported sharing drug equipment or rinse water with other persons; we did not have information on drug-sharing behavior for 1 methamphetamine user with a MRSA SSTI.

In our study population, having had a skin infection within the previous 3 months was the factor most strongly associated with current MRSA skin infection (AOR 7.92, 95% CI 4.10–15.28) (Table 2). Recent sexual contact with someone with a skin infection was also a significant risk factor for MRSA skin disease (AOR 5.42, 95% CI 1.68–17.50), when compared with recent sexual contact with a person without a skin infection. Frequent skin-picking behavior was independently associated with MRSA SSTI (AOR 2.53, 95% CI 1.22–5.23). Crowded living conditions, defined as >1 person per bedroom, had a small but significant association with MRSA SSTI (AOR 1.78, 95% CI 1.004–3.15).

Only 10% of MRSA case-patients had healthcare-associated risk factors traditionally associated with MRSA infection, namely, recent hospitalization, surgery, or dialysis. Additional factors not significantly associated with MRSA SSTI in the study population included use of antimicrobial agents in the previous 6 months, recent stays in a jail or prison, bathing less than daily, history of diabetes or liver disease, recent tattoo or body piercing, and participation in contact sports in the previous 3 months. In addition, very few or no patients were HIV positive (2 [0.5%]), homeless (0), or recently had sex with someone of the same sex (7 [1.6%]), suggesting that none of these were significant risk factors for MRSA SSTI in this population.

The number of visits for \textit{S. aureus} skin infections at one of the main emergency departments in our investigation increased from ≈1 per 1,000 emergency department visits to 12 per 1,000 visits over the 20 months leading up to the investigation (Figure 1). This emergency department accounted for 46.2% of all study participants in our investigation. Over the same period, MRSA infections increased

| Table 1. Demographic characteristics of study participants with (case-patients) and without (controls) skin and soft tissue infections (SSTIs)* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Characteristic                  | Patients with SSTIs | Patients without SSTIs |
|                                 | MRSA (N = 81), no. (%) | MSSA (N = 20), no. (%) | Other† (N = 18), no. (%) | Patients without SSTIs (N = 284), no. (%) |
| Age, y                          | 12 (14.8)         | 0               | 2 (11.1)         | 18 (6.3)       |
| ≤18                             | 30 (37.0)         | 13 (65.0)       | 8 (44.4)         | 102 (35.9)     |
| 19–34                           | 35 (43.2)         | 6 (30.0)        | 7 (38.9)         | 135 (47.5)     |
| 35–64                           | 4 (4.9)           | 1 (5.0)         | 1 (5.6)          | 29 (10.2)      |
| ≥65                             | 48 (59.3)§§       | 8 (40.0)        | 10 (55.6)        | 104 (36.6)     |
| Male sex‡                       |                  |                 |                 |                |
| White                           | 73 (90.1)         | 18 (90.0)       | 16 (88.9)        | 244 (85.9)     |
| Black                           | 5 (6.2)           | 2 (10.0)        | 2 (11.1)         | 36 (12.7)      |
| Other                           | 3 (3.7)           | 0               | 0               | 3 (1.1)        |
| Hispanic ethnicity#             | 2 (2.5)           | 0               | 0               | 4 (1.4)        |

*MRSA, methicillin-resistant \textit{Staphylococcus aureus}; MSSA, methicillin-susceptible \textit{S. aureus}.
†Bacteria other than \textit{S. aureus} isolated from SSTI in our investigation included other \textit{Staphylococcus} spp., \textit{viridans group streptococci}, \textit{Group B Streptococcus}, \textit{Enterobacter cloacae}, \textit{Stenotrophomonas maltophilia}, and mixed flora.
‡6 records did not indicate sex (1 MRSA case, 1 MSSA case, and 4 controls).
§§p<0.0001, when compared with controls.
¶For 1 control, race was not indicated.
#3 records did not indicate ethnicity (2 MRSA cases, 1 other skin infection).
from 2 to 38 per month in the same emergency department. Most emergency department S. aureus cultures for both SSTIs and non-SSTIs were resistant to methicillin, with the prevalence of methicillin-resistance remaining stable over the same 20-month period (median 82%, range 50–100%).

Laboratory Investigation

MRSA (n = 32) and MSSA (n = 13) isolates tested were commonly susceptible to clindamycin, daptomycin, doxycycline, gentamicin, levofloxacin, linezolid, rifampin, tetracycline, trimethoprim-sulfamethoxazole, and vancomycin (Table 3). None of the MRSA isolates and only 1 (7.7%) of the MSSA isolates had inducible clindamycin resistance. MRSA susceptibility patterns of isolates from methamphetamine users and nonusers were similar, except that both MRSA isolates susceptible to erythromycin were found in those who did not use methamphetamine. The MSSA isolate from a methamphetamine user was susceptible to all but penicillin.

We detected genes for PVL in all MRSA isolates and 5 (41.7%) MSSA isolates; however, the MSSA isolate from a methamphetamine user did not carry the PVL locus. All available MRSA isolates from 6 methamphetamine users and 21 nonusers of methamphetamine had type IV SCC mec resistance complex and were PFGE type USA300. Most of the MRSA isolates were a single strain, PFGE type USA300-0114 (4 [66.7%] were methamphetamine users, 15 [71.4%] were non-methamphetamine users) (Figure 2). One third (33.3%) of MRSA isolates from methamphetamine users and one fifth (19.0%) of MRSA isolates from non-methamphetamine users were variants of USA300-0114, such as USA300-0047.

Discussion

MRSA caused over two thirds of all skin infections in the Georgia community we investigated, which is among the highest reported rates of MRSA in SSTI nationwide (16). We found that many previously known risk factors for MRSA skin infection, such as recent skin infection and household contact with someone with a skin infection (19), were common in this population. However, we also identified a novel association between MRSA skin infections and methamphetamine use in a community with a large rural population. Methamphetamine use was reported in nearly 1 in 10 patients with MRSA SSTI and was more common in patients with MRSA skin infections than in patients without skin infections. While most community-associated MRSA SSTI occur in persons without defined risk factors (16), some settings such as prisons and military training facilities appear to facilitate and amplify MRSA transmission (20,21). A similar amplification of transmission may be occurring among methamphetamine users in this community.

Methamphetamine use is associated with a number of socioeconomic and behavioral risk factors that may predispose persons to MRSA SSTI. We found that MRSA SSTI was associated with living with someone with a skin infection, which may increase skin contact with infected persons. Skin-picking was also associated with MRSA SSTI. Methamphetamine use causes formication, a sensa-
tion of something crawling on the body or under the skin, which can lead to skin-picking behavior, skin breakdown, and portals of infection. Other poor hygiene habits that can break the skin, such as fingernail biting, have been associated with MRSA SSTI (12). Methamphetamine use may be associated with limited access to medical care, stays in correctional facilities, and homelessness, all of which have been associated with MRSA SSTI in previous studies (20,22). However, our investigation did not find these to be significant risk factors for MRSA SSTI in this population.

Methamphetamine use has been associated with HIV (23) and sexually transmitted bacterial infections (24), purportedly from increased unprotected sex related to the sexually stimulating property of the drug. A study among urban HIV-positive men who have sex with men found that, in addition to methamphetamine use, use of other sexually stimulating drugs such as nitrates ("poppers") and sildenafil (e.g., Viagra) was associated with MRSA SSTI (12). These previous findings and the results of the current investigation suggest that the use of methamphetamine and other sexually stimulating drugs may increase direct skin-to-skin sexual contact and transmission of MRSA, which can be transmitted through sexual contact (25). We found an increased risk for MRSA SSTI in case-patients who had recently had sex with someone with a skin infection.

Injection of the drug may act as a method of introducing the bacteria into the skin if users fail to clean injection sites or share drug paraphernalia and other potentially contaminated items (26). Injection of methamphetamine can lead to transmission of bloodborne pathogens when injection equipment is shared, as demonstrated in an outbreak of hepatitis B among methamphetamine users in Wyoming (27). A recent case series of 14 patients with MRSA necrotizing fasciitis found that 43% of the patients had current or past injection drug use (28). In contrast to early reports of MRSA in urban injection drug users, our investigation suggested that MRSA skin infections in methamphetamine users are not necessarily due to unclean drug injection. Few methamphetamine users in our population injected the drug or shared equipment; rather, the methamphetamine users in this community commonly smoked or inhaled the drug.

The absolute number of SSTIs at 1 emergency department in this investigation increased during the 18 months preceding the investigation, but the percentage of MRSA isolates was stable over that period. This increase in SSTIs led to a concomitant increase in MRSA SSTIs, which were more common among men, and echoes repeated reports of MRSA SSTI outbreaks in male populations (20,29). This sex difference was not due to increased methamphetamine use in men in our population, since our population of sur-

<table>
<thead>
<tr>
<th>Antimicrobial agent or toxin</th>
<th>MRSA isolates† (N = 32), no. (%)</th>
<th>MSSA isolates (N = 13), no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antimicrobial susceptibility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>32 (100.0)</td>
<td>10 (76.9)‡</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>32 (100.0)</td>
<td>12 (92.3)</td>
</tr>
<tr>
<td>Inducible resistance (D-zone test)</td>
<td>0</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>32 (100.0)</td>
<td>13 (100.0)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>32 (100.0)</td>
<td>13 (100.0)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>2 (6.5)</td>
<td>6 (46.2)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>32 (100.0)</td>
<td>13 (100.0)</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>27 (84.4)</td>
<td>12 (92.3)</td>
</tr>
<tr>
<td>Linezolid</td>
<td>32 (100.0)</td>
<td>13 (100.0)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>0</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>32 (100.0)</td>
<td>13 (100.0)</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>32 (100.0)</td>
<td>13 (100.0)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>32 (100.0)</td>
<td>13 (100.0)</td>
</tr>
<tr>
<td><strong>Toxin gene presence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panton-Valentine leukocidin</td>
<td>32 (100.0)</td>
<td>5 (38.5)</td>
</tr>
<tr>
<td>TSST–1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; TSST, toxic shock syndrome toxin.
†Methicillin resistance was determined by the oxacillin MIC and disk diffusion using a 30-μg cefoxitin disk (14).
‡Three (23.1%) isolates had intermediate resistance to chloramphenicol.
likely re-

Americans in urban centers compared to other races (MRSA) and methicillin-susceptible Staphylococcus aureus (MSSA) isolated from methamphetamine users.

The laboratory investigation found that the most common MRSA strain causing community SSTI was PFGE type USA300-0114, a highly conserved strain that has been implicated in multiple community outbreaks (19). The second most common MRSA strain in this community, and the only other strain found among methamphetamine users, was USA300-0047, which has only a 1-band difference from USA300-0114. MRSA SSTIs in methamphetamine users were not due to a novel or unusual strain of MRSA but rather the most common strain of MRSA in community settings across the United States.

Our investigation is subject to some limitations. First, we did not identify nor do we have data on every SSTI patient who came to the participating clinics and emergency departments for treatment; not every patient with SSTI provided specimens for culture or participated in our survey. Second, we relied on patient report of methamphetamine use and did not conduct drug screens for confirmation. Third, we excluded patients who could only speak Spanish, which may have added to the low number of Hispanic study participants and affected the generalizability of the results. However, Hispanic, foreign-born, and non-English primary speakers each comprise only 5%–10% of the population of these 3 counties (13). Fourth, we were unable to test for other physiologic theories of why methamphetamine may be associated with MRSA, which include weakening the immune system and predisposing users to MRSA carriage by changing the nasal environment. Fifth, we were unable to test whether methamphetamine itself or drug paraphernalia were contaminated with MRSA. Lastly, transmission of MRSA in this population may have occurred in either the community or in the healthcare setting; for some cases, we were unable to determine the origin of the community strains.

Our investigation has direct implications for clinicians. Most clinicians in the participating emergency departments and urgent care clinics did not routinely drain or culture SSTIs. Incision and drainage is a primary therapy for SSTI, and empiric antimicrobial drug therapy may be given in addition to incision and drainage (30). Because of the growing and changing resistance patterns in the community, clinicians should consider culturing SSTI (30). In this population, antimicrobial agents currently recommended for treatment of MRSA (e.g., clindamycin, doxycycline, and trimethoprim-sulfamethoxazole) would be appropriate choices for empiric treatment of outpatient SSTI because of low prevalence of resistance (30). Patients should also be educated about the risks for transmission through household and sexual skin-to-skin contact. Transmission of MRSA in this community is likely due to various factors, and some of these community strains may have been transmitted through healthcare exposure.

Patients with MRSA SSTIs who seek treatment may help clinicians identify a vulnerable population of methamphetamine users. Prevention measures, such as improved hygiene and correct care for wounds, may be helpful when directed at methamphetamine users. However, MRSA SSTIs in methamphetamine users may also impact family and community members who do not use methamphetamine. The same strains of MRSA were circulating among both users and nonusers in our investigation. Public health officials and clinicians should be aware of proper identification, appropriate treatment, prevention of MRSA SSTIs, and the link between methamphetamine use and these SSTIs.

Acknowledgments

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Dr Cohen is a medical epidemiologist in the Respiratory Diseases Branch of the Division of Bacterial Diseases at CDC. This investigation was completed when he was an Epidemic Intelligence Service Officer in the Division of Healthcare Quality Promotion. His primary research interests are the epidemiology of antimicrobial-resistant bacteria, pediatric patient and drug safety, and vaccine-preventable diseases.

References

Methamphetamine Use and MRSA


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