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Risk Factors for Community-Associated Methicillin-Resistant *Staphylococcus aureus* Skin Infections among HIV-Positive Men Who Have Sex with Men

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Abstract

We investigated community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) skin infections among HIV-positive men who have sex with men. We performed a matched case-control study of 35 case patients and 76 control subjects. CA-MRSA skin infections were associated with high-risk sex and drug-using behaviors and with environmental exposures but not with immune status.

Community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is an emerging pathogen distinguished from health care–associated MRSA (HA-MRSA) by clinical, laboratory, and epidemiologic characteristics [1, 2]. Recently, in Los Angeles County, outbreaks attributed to CA-MRSA have been reported among newborns, children, football players, and jail inmates [3–5].

Approximately 30 cases of MRSA skin infection that occurred among HIV-positive men who have sex with men (MSM) were reported to the Los Angeles County Department of Health Services (LACDHS) by infectious disease physicians from an outpatient clinic (the index clinic) during October–November 2002. The hospital reference laboratory performed PFGE on 10 isolates from the index clinic and found that 8 isolates matched and 1 isolate differed by 1 band, indicating a predominant clonal MRSA strain [6]. In response to reports

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from the index clinic and other local clinics, we undertook an investigation of the clinical features, risk factors, and laboratory characteristics of infection.

Methods.

We defined a case as the onset of culture-positive MRSA skin infection (identified in the outpatient setting or within 72 h after hospital admission) in an HIV-positive MSM who had received care at any of 3 participating clinics in Los Angeles County during September 2002–May 2003. For each case, we selected up to 3 control subjects from clinic schedules who were HIV-positive MSM without skin symptoms. Control subjects were matched to case patients on the basis of having the same physician and clinic and having visited the clinic during same week as the case patient's first visit for skin infection. Recruitment was restricted to HIV-infected patients because the participating clinics provided care primarily to HIV-positive MSM, and recruiting adequate numbers of HIV-negative patients from these clinics was therefore difficult.

A patient questionnaire was administered by telephone. For health care–associated risk factors, we asked about exposures during the 12 months before the matched clinic visit. A hospitalization exposure was defined as an overnight hospital stay for any reason other than skin infection. Questions pertained to the previous 3 months for all other potential risk factors and for items regarding demographics. "Close contact" was defined as household contact or sexual contact, which was considered to be intimate skin-to-skin contact. We reviewed medical charts for additional information by use of a standardized chart abstraction form. We followed institutional policy for human subject protection.

Analysis of a variable number of control subjects matched to case patients and logistic regression of multivariate models were performed with the SAS statistical software package, version 8.2 (SAS Institute). Statistical significance was defined as $P < .05$.

A case isolate representing the predominant PFGE pattern from the index clinic was sent to the LACDHS Public Health Laboratory and the Centers for Disease Control and Prevention (CDC) laboratory and was analyzed with PFGE, using *Sma*I [7] for comparison with collected outbreak CA-MRSA strains. The CDC laboratory used PCR primers described by Okuma et al. [8] to determine the staphylococcal cassette chromosome methicillin resistance complex (SCC*mec*) and in-house primers to test for genes for Panton-Valentine leukocidin (PVL), toxic shock toxin, and staphylococcal enterotoxins A–E and H. The isolate was evaluated for inducible clindamycin resistance by use of the standard disk induction ("D-zone") test on Mueller-Hinton agar [9, 10].

Results.

Of 67 case patients who were identified at participating clinics, 42 (63%) completed telephone interviews. Of 110 control subjects selected, 77 (70%) completed telephone interviews. We excluded patients who did not meet case and control definitions after an interview and chart review, and 35 case patients and 76 control subjects were included in the final analysis. Case patients and control subjects were similar demographically and by CD4

cell counts and viral loads, except that case patients were significantly more likely than control subjects to be white (table 1).

Skin lesions were most often diagnosed as abscesses and most often involved the legs, buttocks, and arms (table 2). Among case patients with available data, 15 (52%) of 29 were initially treated with antibiotics that were discordant with antibiogram findings. All case isolates were resistant to the β-lactam antibiotics evaluated. Most isolates were resistant to ciprofloxacin and erythromycin; 1 isolate was intermediately resistant to trimethoprim-sulfamethoxazole. No isolates with resistance to vancomycin, rifampin, or gentamicin were reported.

Case patients were more likely than control subjects to have had close contact with a person who reported having a skin infection, and they were more likely to report routine public hot tub or sauna use (table 3). Other public venues, such as fitness gyms, and activities, such as massage or contact sports, were not significant exposures.

Hospitalization (for any reason other than skin infection) and ciprofloxacin use (prior to infection, for case patients) were associated with MRSA skin infection. Other oral antibiotics were not associated with skin infection, except that trimethoprim-sulfamethoxazole for prophylaxis against opportunistic infection was negatively associated (i.e., protective). Antiretroviral therapy and a history of boils were not associated with infection.

Case patients were less likely than control subjects to report frequent use of disposable seat covers on public toilets and were more likely to report frequent fingernail biting. Other hygiene behaviors and skin trauma (e.g., insect bites, cuts, or abrasions) were not associated with infection.

Case patients were significantly more likely than control subjects to use methamphetamine, nitrates (“poppers”), and sildenafil. Ketamine, cocaine, or gamma hydroxy butyrate were not associated with skin infection. No respondents reported heroin or phencyclidine use. Among drug users, specific drug delivery methods or sharing of drug equipment was not associated with infection.

Neither sexual contact nor the number of sex partners was associated with skin infection. However, among sexually active respondents, case patients were more likely to have 2 or more sex partners and to meet a sex partner in a sex club or bathhouse or via the Internet. Consistent condom use was protective. History of a sexually transmitted infection other than HIV infection was associated with skin infection, but no sexually transmitted infection was specifically associated. Case patients were more likely than control subjects to have attended a group-sex party.

We controlled for hospitalization, race/ethnicity (white race vs. other race/ethnicity), and number of sex partners (categorized as 0, 1, or $\geqslant$2) in the multivariate analysis. Significant exposures included public hot tub or sauna use; methamphetamine use; frequent fingernail biting; professional, hands-on contact with customers at work; and having a sex partner with a skin infection (table 4). Protective exposures included consistent condom use and use of

trimethoprim-sulfamethoxazole for prophylaxis against opportunistic infection. We found similar results after excluding patients with history of hospitalization during the previous 12 months.

The LACDHS Public Health Laboratory determined that an isolate from the index clinic matched the PFGE pattern both of previously collected strains of CA-MRSA from outbreaks in Los Angeles County [11] and of USA300, a CA-MRSA strain identified in several outbreaks nationwide [12]. The CDC laboratory identified genes for PVL and SCC*mec* complex, type IVa. The isolate was clindamycin susceptible and erythromycin resistant and did not exhibit inducible clindamycin resistance.

Discussion.

We found that CA-MRSA skin infections among HIV-positive MSM were associated with high-risk sex and drug-using behaviors but not with immune status. Infections were associated with a clonal CA-MRSA strain that matched PFGE patterns and molecular characteristics (i.e., SCC*mec* IVa and PVL) of outbreak strains within Los Angeles County and elsewhere in the United States [8, 13–16].

Our findings indicate that CA-MRSA spreads by contact transmission—via direct skin-to-skin transmission, such as sexual contact with someone with a skin infection—or by indirect transmission, such as during hot tub or sauna use. Our results are consistent with the findings of other investigations of *S. aureus* infection (e.g., outbreaks mediated by equipment, clothing, or skin-to-skin contact among athletes [4, 17–20] or via communal steam baths used by Alaska Natives [21, 22]). Some risk factors for CA-MRSA in our study, such as white race, multiple sex partners, and sexually stimulating drugs (e.g., methamphetamines), have been associated with high-risk sex behaviors in other studies [23, 24]. Use of injection drugs might also facilitate the introduction of CA-MRSA from colonized skin flora to traumatized skin and soft tissue [25–28].

Our findings are subject to several limitations. First, misclassification of case patients and control subjects might have occurred if control subjects did not report minor skin infections or if clinicians used different criteria for obtainment of wound specimens for culture. Second, we cannot exclude the possibility of bias, because we were unable to match 3 control subjects for each case patient. However, the response rate was typical of outbreak investigations, and case patients and control subjects were demographically similar. Third, we did not have PFGE results for all case patients, so we cannot confirm that all cases were caused by the same CA-MRSA strain. Nevertheless, the clinical, laboratory, and epidemiologic findings are consistent with skin infections caused by a recognized CA-MRSA strain, rather than a HA-MRSA strain. We found antibiotic sensitivity patterns consistent with CA-MRSA. We controlled for hospitalization exposure in the case-control study and found similar multivariate results after excluding patients with a history of hospitalization. Furthermore, our experience with CA-MRSA in multiple Los Angeles County populations [3–5] suggests a broader emergence of CA-MRSA in the community rather than transmission by a point source, such as a hospital.

A majority of patients were initially treated with antibiotics that were discordant with antibiogram findings, indicating the need to increase awareness of CA-MRSA diagnosis and treatment among physicians. Additional research is needed to determine whether empiric treatment of skin and soft tissue infections should be modified among certain populations [29].

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Table 1.

Demographic characteristics of case patients and control subjects in a case-control study of community-associated methicillin-resistant *Staphylococcus aureus* skin infections among HIV-positive men who have sex with men.

Characteristic	Case patients (*n* = 35)	Control subjects (*n* = 76)	*P*[a]
Age, median years (range)	38 (31–57)	40 (22–64)	.139
Race/ethnicity			
Non-Hispanic white	24 (68.6)	34 (44.7)	.013
Hispanic	8 (22.9)	23 (30.3)	.434
Non-Hispanic black	3 (8.6)	13 (17.1)	.072
Asian	0 (0.0)	2 (2.6)	.225
Other	0 (0.0)	4 (5.3)	.248
Insurance status			
No insurance	10 (28.6)	31 (40.8)	.238
Private insurance	10 (28.6)	21 (27.6)	.858
Public insurance[b]	15 (42.9)	24 (31.6)	.231
Unemployed	14 (40.0)	29 (38.2)	.714
History of sexual contact	27 (77.1)	59 (77.6)	.778
CD4 cell count, median cells/mL (range)	338 (<10 to 1424)	409.5 (0 to 1424)	.736
Viral load, median copies/mm^3 (range)	8154 (<25 to 657,000)	594.5 (<25 to 750,000)	.460

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

[a]Cochran-Mantel-Haenszel statistic, stratified by match groupings of case patients and control subjects.

[b]Medicare, Medicaid, or AIDS Drug Assistance Program.

Table 2.

Clinical characteristics and hygiene behaviors of 35 case patients in a case-control study of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) skin infections among HIV-positive men who have sex with men.

Characteristic, by class	Proportion[a] (%)
Clinical characteristic	
Skin lesion diagnosis[b,c]	
Abscess	16/29 (55.2)
Cellulitis	9/29 (31.0)
Furunculosis	8/29 (31.0)
Impetigo	3/29 (10.3)
Folliculitis	2/29 (6.9)
Carbuncle	1/29 (3.4)
Number of lesions at first visit to physician[b]	
1	23/34 (67.6)
2 or more	11/34 (32.3)
Diameter of largest skin lesion at first visit[b]	
≤1 cm	4/24 (16.7)
≥2 cm	20/24 (83.3)
Body area(s) first affected by skin lesions[c]	
Face	2/35 (5.7)
Neck	2/35 (5.7)
Back	4/35 (11.4)
Chest/abdomen	1/35 (2.9)
Armpit	1/35 (2.9)
Arm	4/35 (11.4)
Hand	2/35 (5.7)
Leg	9/35 (25.7)
Foot	1/35 (2.9)
Buttocks	9/35 (25.7)
Groin	2/35 (5.7)
Genitals	3/35 (8.6)
Soft-tissue edema present	15/24 (62.5)
Fever reported at first visit	2/33 (6.1)
Treatment given for MRSA skin lesions[c]	
Oral antibiotics	28/35 (80.0)
Incision and drainage	16/35 (45.7)
Lesion drained by patient	2/35 (5.7)
Surgical debridement	4/35 (11.4)
Hospitalized for MRSA skin infection	7/35 (20.0)

Characteristic, by class	Proportion[a] (%)
Most common antibiotics used for initial outpatient treatment[c]	
TMP-SMZ	9/31 (29.0)
Cephalexin	7/31 (22.6)
Clindamycin	3/31 (9.6)
Intramuscular ceftriaxone	3/31 (9.6)
Intravenous vancomycin as outpatient infusion	2/31 (6.0)
Antibiotic resistance of patient isolates	
Ciprofloxacin	28/31 (90.3)
Levofloxacin[d]	8/31 (25.8)
Erythromycin	26/31 (83.9)
Tetracycline	11/31 (35.5)
Clindamycin	1/31 (3.2)
TMP-SMZ[e]	0/31 (0.0)
Hygiene behavior	
Body areas routinely shaved or clipped prior to skin infection	
Genital region	10/35 (28.6)
Chest	6/35 (17.1)
Anal region	4/35 (11.4)
Armpit	4/35 (11.4)
Hygiene behaviors prior to skin infection	
Shaved or clipped hair in skin area that later developed infection	7/35 (20.0)
Applied personal skin product in skin area that later developed infection[f]	8/35 (22.0)
Shared a personal skin product with another person	6/35 (17.1)
Received a cut or abrasion in the area that later developed skin infection	5/35 (14.3)
Received an insect bite in the area that later developed skin infection	1/35 (2.9)

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] No. of patients with characteristic / no. of patients with data available or no. of isolates with characteristic / no. of total isolates.

[b] Among cases with data available; patients reported diameter to the near-est centimeter.

[c] More than 1 response per respondent was possible for this question.

[d] Twenty-one isolates (68%) had intermediate resistance to levofloxacin.

[e] One isolate had intermediate resistance to TMP-SMZ.

[f] Lotion, over-the-counter skin medication, or skin hygiene product.

Table 3.

Results of bivariate analysis in a case-control study of community-associated methicillin-resistant *Staphylococcus aureus* skin infections among HIV-positive men who have sex with men.

Exposure during the previous 3 months[a]	Proportion[b] (%) of case patients	Proportion[b] (%) of control subjects	Matched OR (95% CI)	*P*[c]
Contact exposure				
Close contact with someone with skin infection	9/35 (25.7)	6/76 (7.9)	3.0 (1.1–8.3)	.040
Sex partner with skin infection	5/35 (14.3)	3/76 (3.9)	4.8 (0.9–27.0)	.073
Close contact with someone who was hospitalized	3/35 (8.6)	8/76 (10.5)	0.8 (0.2–3.3)	.776
Close contact with someone who was incarcerated in jail or prison	5/35 (14.3)	6/76 (7.9)	1.9 (0.5–7.4)	.351
Routine hands-on contact with customers at work	7/35 (20.0)	6/76 (7.9)	2.8 (0.9–9.3)	.085
Routine use of a public hot tub or sauna	19/35 (54.3)	20/76 (26.3)	3.8 (1.4–10.0)	.008
Routine use of a fitness gym	17/35 (48.6)	29/76 (38.2)	1.4 (0.6–3.4)	.386
Past medical history				
Hospitalization overnight or longer, during the previous 12 months	9/35 (25.7)	8/76 (10.5)	3.7 (1.2–11.6)	.027
Drug therapy received				
Ciprofloxacin	5/35 (14.3)	1/76 (1.3)	5.9 (1.1–31.0)	.036
TMP-SMZ for prophylaxis of opportunistic infection	8/35 (22.9)	32/76 (42.1)	0.3 (0.1–0.9)	.031
Antiretroviral therapy	22/35 (62.9)	54/76 (71.1)	0.7 (0.3–1.8)	.506
History of boils ⩾2 times per year	13/35 (37.1)	22/76 (28.9)	1.3 (0.6–2.8)	.544
Hygiene practices				
Frequent use of disposable toilet seat covers	8/35 (22.9)	32/76 (42.1)	0.4 (0.2–1.0)	.047
Frequent fingernail biting	14/35 (40.0)	13/76 (17.1)	2.9 (1.2–6.9)	.020
Illicit drug use				
Methamphetamines	13/35 (37.1)	7/76 (9.2)	6.7 (1.9–24.7)	.004
Nitrates (“poppers”)	9/35 (25.7)	6/76 (7.9)	4.2 (1.4–12.7)	.012
Sildenafil	11/35 (31.4)	11/76 (14.5)	3.3 (1.1–10.1)	.037
Sexual history				
Sex partners,[d,e] median no. (range)	3 (1–120)	1 (1–50)	1.0 (1.0–1.1)	.079
⩾2 sex partners versus 1 sex partner[e]	22/27 (81.5)	28/59 (47.5)	4.4 (1.6–12.3)	.005
Met a sex partner via the Internet[e]	11/27 (40.7)	9/59 (15.3)	5.5 (1.5–20.5)	.011

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Exposure during the previous 3 months[a]	Proportion[b] (%) of case patients	Proportion[b] (%) of control subjects	Matched OR (95% CI)	P[c]
Met a sex partner in a sex club or bathhouse[e]	12/27 (44.4)	10/59 (16.9)	4.0 (1.3–12.9)	.018
Always used a condom during sex[e]	5/27 (18.5)	28/59 (47.5)	0.2 (0.1–0.8)	.015
History of a sexually transmitted infection	9/35 (25.7)	3/76 (3.9)	6.4 (1.7–24.4)	.007
Visited a group sex (circuit) party	6/35 (17.1)	3/76 (3.9)	4.1 (1.1–14.7)	.030

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Unless otherwise stated.

[b] No. of case patients or control subjects with characteristic / no. of patients or subjects with data available.

[c] By χ^2 test.

[d] Continuous variable.

[e] Among sexually active respondents.

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Table 4.

Results of multivariate analysis in a case-control study of community-associated methicillin-resistant *Staphylococcus aureus* skin infections among HIV-positive men who have sex with men.

Exposure during the previous 3 months	Adjusted matched OR[a] (95% CI)	*P*[b]
Sex partner with skin infection	9.2 (1.4–61.5)	.022
Methamphetamine use	8.5 (1.6–45.1)	.012
Routine hands-on contact with customers at work	5.7 (1.2–26.7)	.027
Frequent fingernail biting	4.2 (1.3–14.1)	.019
Routine use of a public hot tub or sauna	3.9 (1.2–12.6)	.023
Use of TMP-SMZ for prophylaxis of opportunistic infection	0.2 (0.1–0.8)	.024
Use of a condom during every sex encounter[c]	0.1 (0.0–0.6)	.019

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Controlling for history of hospitalization during the previous 12 months, race/ethnicity, and number of sex partners (categorized as 0, 1, or ⩾2) during the previous 3 months.

[b] By χ^2 test.

[c] Among sexually active respondents.