

Epidemic Spread of a Single Clone of Methicillin-Resistant *Staphylococcus aureus* among Injection Drug Users in Zurich, Switzerland

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We describe an outbreak of methicillin-resistant *Staphylococcus aureus* (MRSA) among injection drug users (IDUs). From August 1994 through December 1999, we registered 31 IDUs with MRSA infections (12 with soft-tissue infection, 7 with pneumonia [fatal in 1], 7 with endocarditis [fatal in 1], 2 with osteomyelitis, 2 with septic arthritis, and 1 with ulcerative tonsillitis), with a marked increase in the number of IDUs registered during 1998 and 1999. Of 31 patients, 15 (48%) were infected with human immunodeficiency virus. A point-prevalence study among IDUs who frequented outpatient facilities in Zurich revealed an MRSA carriage rate of 10.3% (range, 0%–28.6%) in various facilities. In all but 1 case, pulsed-field gel electrophoresis banding patterns of isolates obtained from these patients were indistinguishable from isolates of the initial 31 IDUs registered. Risk factors for MRSA carriage were disability and prior hospitalization in a hospice. In summary, MRSA became endemic in IDUs in Zurich as a result of the spread of a single clone. This clone caused major morbidity and was responsible for a lethal outcome in 2 cases.

The prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in persons in Switzerland is relatively low, and there is a wide variation in prevalence (range, 0%–21%) between different hospitals in Switzerland [1]. As in most parts of the world, MRSA transmission occurs mainly among hospitalized patients. Transmission of MRSA to the general population may originate from patients who remain colonized after discharge or

from health care workers. Transmission in the other direction is also possible and was reported in 1982 [2]. An epidemic of MRSA infection occurred among users of parenteral drugs in Detroit. This epidemic originated in the community, but the pathogen was later found in several hospitals and nursing homes, and it resulted in an increase in the rate of nosocomial MRSA infections.

The number of injection drug users (IDUs) in Zurich, Switzerland is substantial [3]. Many have multiple contacts with various medical facilities. Infections caused by *S. aureus* are common among IDUs [4] and result in considerable morbidity. In the present study, we report on the prevalence of MRSA and on an epidemic of MRSA in a cohort of IDUs in Zurich.

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METHODS

Clinical setting and MRSA surveillance. The University Hospital of Zurich (UHZ) is a 1000-bed hospital that, in addition to its academic mission to provide tertiary care, provides primary care to the inhabitants of the Zurich metropolitan area. Primary care is also provided by 2 city hospitals. These hospitals, as well as the orthopedic university hospital and a hospice in the downtown area, collaborate closely with the hospital epidemiology (HE) unit of UHZ and send all MRSA isolates to the HE laboratory at UHZ. All MRSA cases in the Zurich area have been prospectively registered since 1993, as part of the surveillance activities of the HE unit of UHZ. MRSA isolates are subjected to molecular genotyping. Physicians who take care of patients infected with MRSA of the genotype responsible for this outbreak were contacted (see Evolution of MRSA epidemic section), and the medical records of these patients were reviewed retrospectively for demographic and clinical data. Demographic data included age and sex. Clinical data included the type of infection and underlying illnesses, including HIV infection, and the presence and degree of cellular immunodeficiency.

Survey of MRSA prevalence. To determine the prevalence of MRSA carriage and/or infection among IDUs in the city of Zurich, we conducted a prospective, clinical-epidemiological study in July and August 1999. A hospice with a dispensary (Sune-Egge), a dispensary for the homeless (KFO), a drug rehabilitation clinic (Frankental), 2 facilities that distribute drugs and allow injection of drugs under controlled circumstances (Crossline and Lifeline), and 6 drug-injection facilities were included. Drug-injection facilities provide a hygienic environment (including distribution of needles and syringes) in which IDUs are permitted to inject drugs purchased on the street.

Approximately two-thirds of IDUs agreed to screening of anterior nares with the use of swabs, to determine nasal carriage of MRSA. A standardized questionnaire was used to collect information on sociodemographic factors, type and frequency of drug use, presence of medical disability, type of interactions with other IDUs, living conditions (e.g., apartment, shelter, or homeless), and any hospitalizations that occurred during the preceding 6 months.

Microbiological studies and genotyping. Nose swabs were immediately introduced into a transport medium (Stuart medium). Cultures were performed on sheep blood agar and were incubated for 24 h at 35°C. Identification of *S. aureus* was based on the morphology of colonies, typical Gram staining, and a positive result of a catalase test and was confirmed with the use of Staphaurex (Murex Diagnostics). Antimicrobial susceptibility testing was performed according to the guidelines of the National Committee for Clinical Laboratory Standards [5], by means of disk diffusion methodology with Mueller-Hinton agar (Oxoid) and oxacillin disks (1 µg). The zone-diameter breakpoints for isolates susceptible or resistant to oxacillin were ≥ 13

mm and ≤ 10 mm, respectively. Mupirocin disks (5 µg) were used to determine susceptibility to this compound. The zone-diameter breakpoints for isolates susceptible or resistant to mupirocin were ≥ 14 mm and ≤ 13 mm, respectively [6].

Each MRSA isolate was confirmed with MRSA-Screen (Denka Seiken), a slide latex agglutination kit for the rapid detection of penicillin-binding protein 2. PCR analysis of random isolates was done to determine the presence of the *mecA* gene. Molecular analysis of each isolate was done by pulsed-field gel electrophoresis (PFGE) with the use of *Sma* I restriction enzyme, by use of a CHEF-DR III system (Bio-Rad). Initial switch time was 1 s, final switch time was 45 s, and the run time was 24 h at 6 V/cm. Gels were stained with ethidium bromide and viewed by ultraviolet transillumination, and the pattern of restriction fragment bands was interpreted. Isolates were considered to be the same strain according to the criteria published by Tenover et al. [7].

Statistical analysis. Categorical variables were analyzed with Fisher's exact test. Continuous variables were analyzed with Student's *t*-test. $P < .05$ was considered statistically significant. All tests were 2-sided. Computations were performed with use of Statview software (version 4.5; Abacus Concepts).

RESULTS

Evolution of MRSA epidemic. From August 1994 through December 1999, we registered 31 IDUs with MRSA infection. MRSA isolates were recovered sporadically from IDUs during 1994–1997, whereas a marked increase was noted during 1998–1999 (figure 1). During the same period, the number of IDUs seen at the involved hospitals did not change significantly from year to year. Clinically relevant infections that required hospitalization were noted in all patients (table 1). Of the 31 patients, 15 (48%) were infected with HIV and had various

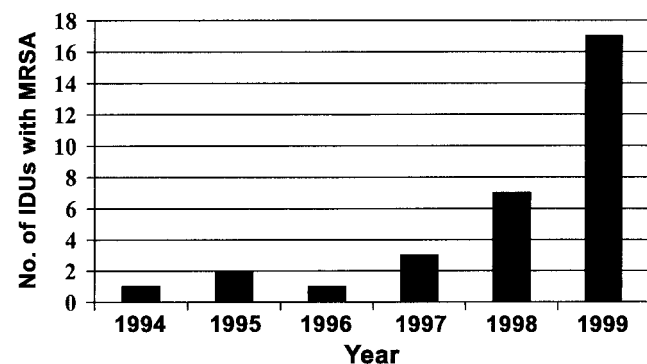


Figure 1. The number of injection drug users (IDUs) with newly detected methicillin-resistant *Staphylococcus aureus* (MRSA) per year is shown. Presence of MRSA was detected in clinical specimens, usually at the time of manifest infection. Cases detected during the prevalence survey are not included in this figure.

Table 1. Clinically relevant infections in patients infected with methicillin-resistant *Staphylococcus aureus*.

Type of infection	No. of patients (n = 31)	Patient age, mean y (range)	Sex of patients, no. of males:no. of females	Comment
Wound or soft-tissue infection	12	36.0 (26–42)	9:3	Complications of drug injections
Pneumonia	7	35.3 (28–43)	4:3	2 patients with sepsis, 1 with empyema, 1 with fatal outcome
Endocarditis	7	41.1 (27–58)	5:2	1 patient with fatal outcome
Osteomyelitis	2	34.5 (30–39)	1:1	Vertebral column and pelvis were affected
Septic arthritis	2	34.5 (31–38)	1:1	Knee and hip joint were involved
Ulcerative tonsillitis	1	30	0:1	Unilateral tonsillitis

degrees of cellular immunodeficiency, with CD4⁺ lymphocyte counts ranging from 53/ μ L to 769/ μ L.

After the discovery of the outbreak, a hospice for IDUs (Sune-Egge) in downtown Zurich was recognized as a potential site for the spread of MRSA. Screening of all hospice patients in October 1998 revealed nasal carriage of MRSA in 12.5% (3 of 24 patients).

Susceptibility and genotype of MRSA isolates. All MRSA isolates were susceptible to mupirocin, clindamycin, and gentamicin or netilmicin; 30 of 31 isolates were susceptible to rifampin; and 29 of 31 isolates were susceptible to ciprofloxacin. However, 24 of 31 were resistant to cotrimoxazole. All 31 isolates had identical banding patterns by PFGE.

Point-prevalence study. A point-prevalence survey performed from July through August 1999 involved a total of 280 swab specimens obtained from the anterior nares of 224 IDUs and 56 health care workers at the 12 study locations. *S. aureus* was identified in 94 (33.6%) of these specimens. These isolates originated from 79 IDUs (carriage rate, 35.3%) and 15 health care workers (carriage rate, 26.8%). None of the isolates recovered from health care workers was resistant to methicillin. Of the 224 IDUs, 23 (10.3%) had nasal cultures that were positive for MRSA, which accounted for 29.1% of *S. aureus* isolates (23 of 79). A single isolate was resistant to mupirocin on Mueller-Hinton agar.

The prevalence of MRSA colonization varied markedly between the different facilities. Prevalence was 23.3% in the hospice and 28.6% in 1 of the drug-injection facilities. In other facilities, prevalence varied from 0% to 15%.

Transmission of the outbreak strain. Molecular genotyping by PFGE of MRSA isolates revealed that 22 isolates belonged to a single clone and that the banding pattern was indistinguishable from the pattern recognized during the initial epidemic. A different pattern was found for only 1 IDU from 1 of the drug-injection facilities. MRSA that belonged to the same genotype was isolated from the wound of a patient who had been hospitalized in the radio-oncology unit of the University

Hospital of Zurich at the same time as one of the patients who belonged to the cohort of IDUs. Although no epidemiological links could be established between these 2 patients, nosocomial transmission of MRSA from the IDU to the second patient on the radio-oncology unit can be assumed on the basis of the temporal association of the hospital stays of these patients. Before the current epidemic, this strain had not been detected in other patients hospitalized at any of the hospitals in the greater Zurich area.

Risk factors for colonization. Of all the factors considered in the analysis of risk factors for colonization (table 2), pension for disability and prior hospitalization at the hospice were significantly more common among MRSA carriers.

DISCUSSION

This study shows that a single clone of MRSA is currently endemic in IDUs in Zurich, that this clone is responsible for an ongoing outbreak, and that it may spread secondarily to other patient groups. This outbreak poses serious problems for various health care facilities in the Zurich metropolitan area.

The association between MRSA and injection drug use is not new. In 1982, Saravolatz et al. [4] reported 165 patients with infections caused by community-acquired MRSA at Henry Ford Hospital (Detroit). The proportion of community-acquired *S. aureus* infections resistant to methicillin at Henry Ford Hospital rose from 3% in March 1980 to 38% in September 1981. Injection drug use was associated with the development of this infection [4]. Ten years later, MRSA accounted for 47% of the isolates obtained from 101 IDUs with *S. aureus* infection at the same tertiary-care hospital [8]. In Spain, a country with a high rate of MRSA in hospitals [9], MRSA was not endemic in IDUs in 1992. Rubio et al. [10] analyzed 311 episodes of *S. aureus* bacteremia during a 4-year period. Endocarditis in IDUs was responsible for 53 of these bacteremia episodes. However, in these patients, MRSA was rare.

Nasal colonization with *S. aureus* is epidemiologically linked

Table 2. Characteristics of injection drug users (IDUs) colonized with methicillin-resistant *Staphylococcus aureus* (MRSA) versus those of IDUs not colonized with MRSA.

Characteristic	IDUs colonized with MRSA (n = 23)	IDUs not colonized with MRSA (n = 201)	P
Sex			
Male	15/23 (65)	156/197 (79)	.18
Female	8/23 (35)	41/197 (21)	
Age mean $\bar{y} \pm$ SD	36 \pm 4	33 \pm 9	.125
Drug use			
Within a group	7/16 (44)	37/155 (24)	.13
Usually alone	9/16 (56)	118/155 (76)	
Circumstances of living			
Apartment	18/23 (78)	141/201 (70)	>.2
Therapy group	0	13/201 (6.5)	>.2
Shelter	3/23 (13)	19/201 (9.5)	>.2
Homeless	2/23 (9)	28/201 (14)	>.2
Employment status			
Regular job	1/23 (4)	28/200 (14)	>.2
Occasional job	2/23 (9)	30/200 (15)	>.2
Unemployed	7/23 (31)	73/200 (36.5)	>.2
Pension for disability	13/23 (56)	69/200 (34.5)	.04
No hospitalization during 1999	12/23 (52)	88/177 (49.7)	>.2
Hospitalizations during 1999			
University Hospital	4/14 (28)	25/115 (22)	>.2
Waid City Hospital	1/14 (7)	5/115 (4)	>.2
Triemli City Hospital	1/14 (7)	12/115 (10)	>.2
Sune-Egge (Hospice)	8/14 (57)	35/115 (30)	.07 ^a
Other	0	38/115 (33)	.01

NOTE. Data are n/N (%) of patients, unless otherwise indicated.

^a P = .045 by Pearson's χ^2 test.

to an increased risk of subsequent infection [11, 12]. In IDUs, it also appears to predispose to infection by providing a reservoir from which the skin is seeded [13]. Frequent needle injections without proper antiseptic technique provide a portal of entry [13]. A similar association between nasal carriage and an increased risk for invasive infections was reported for HIV-infected patients [14].

We therefore studied the prevalence of nasal MRSA carriage in a cohort of IDUs in Zurich. The prevalence of MRSA nasal carriage in our population was 10.3%, and MRSA accounted for 29.1% of *S. aureus* isolates. There was a wide range in prevalence of MRSA among the different facilities (0% in a suburban facility and up to 28.6% in downtown facilities). The reason for these differences in prevalence of MRSA is unknown. It may be speculated that IDUs who frequent a drug-injection facility in one of the suburbs of Zurich have only rare contacts with IDUs at facilities in the downtown area.

Studies in other geographic locations showed markedly lower

prevalence rates. From March 1994 through May 1995, Holbrook et al. [15] studied 217 current and former drug addicts who were recruited from a hospital-affiliated methadone-maintenance program in the Bronx, New York, for an ongoing longitudinal study of the natural history of HIV disease. Nasal cultures were positive for *S. aureus* for 41% of the subjects. The antibiotic susceptibility patterns were similar to those of the isolates obtained from outpatients at the local hospital and included 2.3% MRSA. No dominant strain was identified by arbitrarily primed PCR analysis [15]. Dan et al. [16] studied the carriage of MRSA in nonhospitalized subjects in Israel. In 350 drug users who attended a methadone clinic, the isolation rate of *S. aureus* was 9.1% (n = 32), and only 2 IDUs (0.6%) had nasal colonization with MRSA [16]. Genotyping was not done.

In our study, the high prevalence of MRSA in IDUs was caused by the local spread of a single clone. This is in contrast to the findings reported by Layton et al. [17], who described

the epidemiology of MRSA at a university hospital in New Haven, CT. Among 87 patients with MRSA, 36 had community-acquired infections, which were associated with injection drug use in 6 cases. PFGE allowed differentiation of 35 distinct DNA patterns; heterogeneity was seen among both nosocomial and community-acquired isolates, with few instances of cross-transmission.

The mechanism of spread of the epidemic strain among IDUs in Zurich is unclear. MRSA carriers had a higher rate of hospitalizations in a hospice in downtown Zurich and included more recipients of pension for disability. This may be interpreted as a marker for prolonged drug use. Craven et al. [18] had previously noted that chronic drug use is a reason for the use of "shooting galleries" by IDUs. MRSA carriers also had a higher rate of drug use within a group rather than alone, but this difference was not statistically significant. Frequent and close contacts may be a source of person-to-person transmission of MRSA. For instance, Lindenmayer et al. [19] reported the transmission of MRSA among healthy participants on a high school wrestling team.

Furthermore, needle-sharing can facilitate transmission of an epidemic strain. Craven et al. [18] reported 7 episodes of MRSA endocarditis. All patients patronized a local "shooting gallery," where paraphernalia were provided and drugs were often administered by a "street doctor." All isolates were the same phage type [18]. HIV-infection prevention strategies reduced this behavior among drug users. An older study at the Detroit Medical Center suggested that one brand of heroin served as a common source [20]. Saravolatz et al. [2] found that culture results for heroin samples provided by drug users with MRSA infection were negative, which is consistent with findings of previous investigators, who were unable to recover significant pathogens when culturing heroin [21]. Since there were no significant differences regarding drug-use behavior between carriers of MRSA and noncarriers in our study population, we consider heroin or cocaine to be very unlikely sources of this outbreak. Given the particular living conditions of many IDUs, frequent and close social contacts appear to be the most likely explanation for the observed spread of MRSA in this cohort.

MRSA is not the only bacterial agent that causes epidemic outbreaks among IDUs. Recently, an outbreak of a single clone of nontoxigenic *Corynebacterium diphtheriae* that caused infections among drug users in Zurich was reported. A total of 38 of 65 patients from whom *C. diphtheriae* had been isolated from 1990 through 1996 were IDUs. Skin infections were documented in 15 patients, respiratory infections in 10, and bacteremia in 13 (including 9 patients with endocarditis, 4 of whom died). The same ribotype of nontoxigenic *C. diphtheriae* was found in 31 of the 32 examined isolates associated with injection drug use [22]. Shekar et al. [23] described an outbreak

of endocarditis caused by *Pseudomonas aeruginosa* serotype 011 among abusers of pentazocine and tripeleminamine in Chicago.

Because IDUs have multiple contacts with various medical facilities [24], it is important to eradicate MRSA in this population to prevent the spread of MRSA within institutions such as dispensaries and hospices, as well as the spread to community and university hospitals. Spread of MRSA into health care facilities carries the potential for secondary spread to non-IDUs. This has occurred at least once at the University Hospital of Zurich, as a result of the current outbreak. Larger outbreaks that involve transmission of MRSA to hospitalized HIV-infected patients have been reported from the United Kingdom [25] and Spain [26].

In summary, we observed a marked increase in MRSA among IDUs in the Zurich area. This increase was caused by the local spread of a single clone. The observed MRSA clone caused significant morbidity in this group of IDUs. MRSA is currently endemic among IDUs in Zurich. The emergence of MRSA in IDUs in Zurich poses risks for spread in the inpatient and outpatient settings, because of the persistence of colonization that may go unrecognized for a prolonged time.

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