Community-Adapted Methicillin-Resistant Staphylococcus aureus (MRSA): Population Dynamics of an Expanding Community Reservoir of MRSA

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To define methicillin-resistant Staphylococcus aureus (MRSA) reservoirs in the community and their population dynamics, we studied the molecular epidemiology of a random sample (n = 490) from a collection of 2154 inpatient and outpatient MRSA isolates during a 7-year period in San Francisco. We noted a progressive replacement of type II staphylococcal chromosomal cassette (SCC)meC–bearing isolates with type IV SCCmeC–bearing isolates, which coincided with a 4-fold increase in methicillin resistance between 1998 and 2002. Type IV SCCmeC–bearing isolates involved in the increase in methicillin resistance belonged to 4 molecular genotypes. These 4 genotypes were associated predominantly with community-onset disease, rather than hospital- or long-term-care facility–onset disease (76.9% vs. 19.4% vs. 3.7%; P < 0.0005), suggesting that they are not feral descendants of hospital isolates. The longitudinal results linked the dramatic increase in MRSA infections to an expanding community reservoir of MRSA genotypes with intrinsic community survival advantage.

Hospitals, long-term-care facilities (LTCFs), and similar institutional settings have been traditional strongholds of methicillin-resistant Staphylococcus aureus (MRSA). Recent reports of community-associated MRSA infections among children with no health care–associated risk factors provided the first evidence of the existence of a true community MRSA reservoir that is independent of the hospital [1, 2]. Subsequently, community-associated MRSA disease has been identified in clusters throughout the United States [3–13]. These observations provide support for the view that there is community-associated MRSA disease arising with some frequency among community-dwelling individuals with no antecedent hospital exposure. However, the extent of MRSA disease that is endemic in community settings is not known.

Traditionally, community-onset (CO-MRSA) and nosocomial-onset MRSA (NO-MRSA) isolates have been differentiated on the basis of time after admission to the hospital [14, 15]. Isolates cultured from patients within the first 48–72 h of hospitalization or from patients in an outpatient setting have been classified as “community onset.” This term conveys the difficulty in demonstrating that a CO-MRSA isolate was not acquired as a result of a recent visit to a health care facility or close contact with a patient who has been recently discharged. Efforts to identify the origins of CO-MRSA on the basis of risk factors of prior exposure to the health care system make the assumption that contacts with health care facilities have resulted in productive patient colonization by strains endemic in hospitals [16, 17]. However, prior health care exposure may be a
potential confounder in the relationship between prior MRSA acquisition and community-onset disease. Community-onset disease may not be caused by feral descendants of hospital isolates at all, but, rather, outpatient antibiotic use, immunocompromised status due to HIV/AIDS, long-term intravenous access, or other iatrogenic reasons may predispose these health care users to become colonized and infected by a true community-dwelling pathogen. By discounting the possible community origin of CO-MRSA cases with health care–associated risk factors, the extent of the MRSA reservoir in the community may be substantially underestimated.

The analysis of CO-MRSA isolates from patients lacking health care–associated risk factors identified 4 features that differentiate CO-MRSA from NO-MRSA isolates: (1) they are susceptible to most antibiotics other than β-lactams [1, 18]; (2) they carry the type IV staphylococcal chromosomal cassette (SCC) element encoding β-lactam resistance [19, 20]; (3) they carry toxins such as Panton-Valentine leukocidin (PVL) and other enterotoxins [11, 16, 21–23]; and (4) they are not related to genotypes that are endemic in hospitals [16, 17, 21, 23, 24]. The recent emergence of distinct community strains emphasizes the dynamic structure of MRSA populations and the importance of genotypic characterization in defining relationships between hospital and community strains.

We describe here the population dynamics of community and hospital MRSA isolates associated with a dramatic increase in MRSA infections detected by the Community Health Network (CHN) of San Francisco over the 7-year period during 1996–2002 [10, 11, 17]. Inpatient and outpatient MRSA isolates identified through hospital-based surveillance were characterized with respect to their clinical and molecular epidemiology. This longitudinal collection of clinical isolates afforded a unique opportunity to investigate the origins of community and hospital MRSA strains.

MATERIALS AND METHODS

Setting. From January 1996 through December 2002, the Molecular Epidemiology Research Laboratory (MERL) collected 2154 clinical MRSA isolates originating from unique patients for the infection control and surveillance services that it provides to CHN. CHN includes the San Francisco General Hospital (SFGH) and clinics, Jail Health Services, an LTCF, and 13 satellite outpatient clinics. Isolates originating from 1 of the outpatient clinics, the Integrated Soft Tissue Infection Services (ISIS) clinic, which specializes in the surgical treatment of skin and soft tissue infections (SSTIs), were excluded from the present study, to avoid any overrepresentation of cultures from SSTI sites that are not routinely performed. Isolates recovered from the ISIS clinic were characterized in a different study that investigated widespread SSTIs in San Francisco [11].

Selection of samples. Given the large number of isolates, a random, uniform, stratified sample of 70 isolates/stratum-year, 1996–2002 (n = 490), was selected for detailed analysis. The nonproportional selection oversampled isolates (relative to the total number of isolates per year) during the early years of the study, to efficiently increase the accuracy of the estimates of the population parameters of interest for those periods [25]. Computerized records were reviewed to abstract information on patient health care use, such as prior hospital admission (to SFGH) and/or prior outpatient facility visits (emergency department, satellite clinics, or jails) within 2 years of the date of MRSA culture collection. The specimen sources from which MRSA originated were also ascertained, and these were classified into 5 main groups: (1) sterile sites, including blood, cerebrospinal fluid (CSF), and bone; (2) SSTIs, including skin, abscess, wound, lesion, eye, pustule, tissue, nose, and ulcer; (3) respiratory sites, including tracheal aspirates, sputum, and induced sputum; (4) urine; and (5) others, including all other clinical sites, such as fluid of unspecified origin, ear, and gallbladder.

Definitions. A CO-MRSA isolate was defined as an MRSA-positive culture from a clinical specimen obtained from an outpatient or within the first 72 h of hospital admission. An NO-MRSA isolate was defined as a positive culture obtained after 72 h of hospital admission. Patients living in LTCFs were analyzed as a separate group.

Antimicrobial susceptibilities. CHN’s centralized clinical laboratory, based at SFGH, performed all original cultures and antimicrobial-susceptibility testing. MIC determinations were performed for ciprofloxacin, tetracycline, gentamicin, erythromycin, cotrimoxazole, rifampin, clindamycin, and vancomycin by use of the Microscan Walkaway instrument (Dade International), according to NCCLS guidelines [26]. Multidrug resistance was defined as resistance to ≥3 non-β-lactam antibiotics.

Molecular typing. All 490 isolates were genotyped by use of pulsed-field gel electrophoresis (PFGE) with Smal, as described elsewhere [27]. A subset of 61 MRSA isolates with divergent PFGE patterns (>6 bands different from all other isolates) were further characterized by multilocus restriction-fragment typing (MLRFT) [28]. MLRFT assesses restriction-site variations in the same 7 housekeeping gene fragments as those used for multilocus sequence typing (MLST); this method provides a low-cost alternative for rapidly clarifying divergent PFGE patterns. To provide a uniform nomenclature for describing MRSA, MLST [29] was performed on representative isolates from each concordant PFGE-MLRFT–defined genotype; sequence types were assigned with reference to the MLST database (http://www.mlst.net).

The structural features unique to each of the 4 major allelotypes of the SCCmec element, types I–IV [19, 30], were determined by a polymerase chain reaction–based multiplex assay described elsewhere [31]. Unique SCCmec type patterns not consistent with those described by Oliveira and de Lancaster
were further characterized by use of the method of Okuma et al. [24], to determine the ccr gene and the mec gene complex.

**Statistical methods.** To account for the nonproportional, stratified, random sampling design (70 random isolates/stratum-year), the survey data analysis function in Stata software (version 8; Stata) was used to compute estimates and significance levels for the entire strain population, with appropriate weighting to restore the original proportions.

**RESULTS**

**Clinical epidemiology of MRSA cases.** A total of 2154 clinical MRSA isolates were collected from unique patients over the 7-year period during 1996–2002. The number of unique MRSA isolates increased from 160 in 1996 to 563 in 2002 (figure 1A). For the present study, 70 isolates from each year were randomly selected (n = 490) for detailed analysis.

The number of NO-MRSA or LTCF-MRSA infections remained relatively stable during the 7-year sampling period (figure 1A). In contrast, there was a statistically significant increase in the number of CO-MRSA infections during the 7-year period that matched the temporal increase in the total number of MRSA infections (figure 1A; P = .0001, χ² test for trend). By use of the MRSA levels in 1996–1997 as a baseline, 82.0% of the total number of MRSA infections during 1998–2002 above that baseline can be attributed to CO-MRSA infections. The vast majority of the CO-MRSA infections originated in patients who had previously been hospitalized (65.2%) or had been treated in an outpatient setting (25.4%) within the preceding 2 years; only 9.4% of patients with CO-MRSA infections had no history of health care exposure.

Cases of CO-MRSA infection were significantly more likely to involve an SSTI than were NO-MRSA and LTCF-MRSA infections (59.3% vs. 23.7% vs. 29.8%; P = .0001). Cases of CO-MRSA infection were as likely as those of NO-MRSA infection to be more serious and to involve blood, CSF, or bone, which suggests no difference in the pathogenic potential of CO-MRSA versus NO-MRSA isolates. Only 4.7% of LTCF-MRSA infections originated from sterile-site infections. The isolation of MRSA from urine and respiratory sites was higher for NO-MRSA (17.6% and 31.6%, respectively) and LTCF-MRSA (29.6% and 30.2%, respectively) than for CO-MRSA (9.0% and 12.2%, respectively) infections (P = .0001).

**SCCmec typing and antimicrobial susceptibilities.** The SCCmec types were assessed in all 490 clinical MRSA isolates (see table 1). Almost all of the isolates carried either the type II (33.3%) or type IV (64.6%) SCCmec element. Type I SCCmec was found in 1 isolate and type III SCCmec in 2 isolates. Nine isolates exhibited novel SCCmec patterns that did not match the archetypal type I–IV SCCmec patterns described by Oliveira and de Lancastre [31] and Okuma et al. [24]. The number of isolates bearing type II SCCmec remained relatively stable across stratum-year, except during 2001–2002, when the number of MRSA infections increased as the result of an outbreak caused by an isolate carrying the type II SCCmec element (figure 1B) [32].

Beginning in 1998, the proportion of isolates harboring the type IV SCCmec element increased rapidly (figure 1B). This coincided with the temporal increase in the number of CO-MRSA infections (figure 1A); in fact, 98.8% of the CO-MRSA infections above the baseline level of 1996–1997 could be attributed to isolates bearing the type IV SCCmec element. Types II and IV SCCmec carriage in NO-MRSA isolates was approximately equally distributed (47.6% vs. 52%), but type II SCCmec predominated in LTCFs, which accounted for 81.6% of LTCF-MRSA isolates.

Type IV SCCmec isolates were less likely than type II isolates to be multidrug resistant (MDR; 7.0% vs. 91.9%, P = .0001).

**Figure 1.** Secular trend of clinical methicillin-resistant *Staphylococcus aureus* (MRSA) isolates at the Community Health Network of San Francisco. Distribution of isolates according to location of disease onset: community onset (CO), nosocomial onset (NO), long-term care facility onset (LTCF), and all locations (total MRSA-observed count) (A); and types II and IV staphylococcal chromosomal cassette (SCC)mec (B). The isolate count estimates had been weighted appropriately to account for the nonproportional, stratified, random sampling design.
Table 1. Antibiotic susceptibilities and molecular characterization of clinical methicillin-resistant *Staphylococcus aureus* (MRSA).

<table>
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<th>Genetic typing marker</th>
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<th>MLRFT (allele profile)</th>
<th>PFGE</th>
<th>SCC mec</th>
<th>Estimated % of total</th>
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<th>% MDR</th>
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**NOTE.** Isolates with similar pulsed-field gel electrophoresis (PFGE) patterns (6-band difference) received the same letter designation, to reflect their genetic relatedness (e.g., C, P, S, and Z); highly divergent PFGE patterns are designated as unique (U) types (U1, U2, and U3). High-frequency (>5% of the total no. of isolates) genotypes are underlined. Percentages of resistant isolates are listed for gentamicin (GEN), ciprofloxacin (CIP), clindamycin (CLI), erythromycin (ERY), trimethoprim-sulfamethoxazole (SXT), and tetracycline (TET). No isolates were resistant to vancomycin. MDR, multidrug resistant; MLRFT, multilocus restriction-fragment typing; MLST, multilocus sequence typing; SCC, staphylococcal chromosomal cassette.

**a NT1 and NT2 were 2 SCC mec patterns that did not match the type I–IV SCC mec patterns described by Oliveira et al. [31].** On the basis of a different polymerase chain reaction (PCR)-based allotyping of ccr and mec complexes [24], the 2 defining features of an SCC mec allotype, the NT1 pattern (6 isolates) contained ccr type 2 and a nontypeable mec complex element. The NT2 pattern (3 isolates) did not show PCR amplification when primers for the ccr and mec complex genes were used.

**b The total refers to the entire collection of 2154 isolates, with percentages corrected for the nonproportional stratified sampling design.**

Similarly, CO-MRSA isolates were less likely than NO-MRSA or LTCF-MRSA isolates to be MDR (19.0% vs. 51.0% vs. 77.0%, respectively; \( P = .0001 \)).

**Genotypic characterization.** All 490 MRSA isolates were genotyped by PFGE (table 1). A subset (n = 61) was further screened by MLRFT [28] to clarify relatedness of divergent PFGE patterns. On the basis of PFGE and MLRFT results, 16 unique genotypes were identified. Of these, 8 genotypes were associated with >2 different SCC mec types, which suggests multiple independent acquisitions of SCC mec within each clonal lineage. The 16 unique MLRT-PFGE-defined genotypes were further characterized by MLST [29], to provide a standardized nomenclature. For brevity, a clonal type was identified by its MLST and PFGE types (e.g., ST30:Z).

**Predominant CO-MRSA genotypes.** The vast majority (96.4%) of CO-MRSA infections above the baseline level of 1996–1997 were associated with 4 clonal types: ST8:C, ST8:S, ST59:P, and ST30:Z (figure 2A). All 4 clonal types carried the type IV SCC mec element.

ST8:C belongs to the ST8 complex, one of the most successful pandemic MRSA types [33]. ST8:C was present in the 1996–1997 baseline sample and more than doubled in prevalence between 1998 and 2002, accounting for 15.8% of the total number of CO-MRSA infections above the baseline level (figure 2A). The prevalence of ST8:C did not change significantly across stratum-year among NO-MRSA and LTCF-MRSA infections (figure 2B and 2C). Although most ST8:C isolates carried the type IV SCC mec element, some ST8:C isolates were found to
Figure 2. Strain distribution by location of disease onset. A, Community onset; B, nosocomial onset; and C, long-term-care facility onset. Strain attributes are designated according to multilocus sequence typing, pulsed-field gel electrophoresis, and staphylococcal chromosomal cassette mec type. The Y-axis shows the estimated no. of isolates for the entire strain population, with appropriate weighting to account for the non-proportional, stratified, random sampling of 70 isolates/stratum-year.

carry type II SCCmec and to be MDR; more than one-half (53.6%) of these isolates were recovered from cases of NO-MRSA and LTCF-MRSA infection. Type II SCCmec–bearing ST8:C isolates were not recovered from 2000 onward.

A second genotype in the ST8 complex, ST8:S, has recently emerged in our community. ST8:S shares only 9 of 15 PFGE bands with ST8:C (see [11] for PFGE banding patterns; ST8:S corresponds to USA300 and ST8:C to USA500, as described by McDougal et al. [34]). ST8:S was first identified in September 2000 in an outpatient with an SSTI [10]. The rapid emergence of ST8:S in this community is evident: it accounted for 29.7% (182/612) of the total number of CO-MRSA infections during 2001–2002 (figure 2A). The first inpatient case of ST8:S infection was identified in June 2001, and, by the end of the survey period in December 2002, ST8:S accounted for an estimated 14.1% (29/206) of NO-MRSA infections (figure 2B). Thus, it appears that ST8:S initially emerged in the community and spread from there into the hospital. ST8:S was not detected in the random sample of LTCF-MRSA infections. However, routine genotyping for surveillance purposes identified the earliest ST8:S in an LTCF in November 2001.

ST59:P was detected in both CO-MRSA and NO-MRSA isolates throughout the survey period. However, a subtype of ST59:P, designated ST59:P∗, was first identified in 1999 and accounted for an estimated 172 cases of CO-MRSA infection (20.8% of total CO-MRSA infections above the baseline level) and 65 cases of NO-MRSA infection by the end of the survey period (figures 2A and 3B), attesting to its enhanced capacity for community survival. ST59 has been described infrequently in worldwide collections (see http://www.mlst.net) [28, 35]. Other subtypes of ST59:P, found predominantly among NO-MRSA, were not seen in our collection from 1999 onward. ST59:P was not recovered from any LTCF (figure 2C).

Between 1998 and 2002, a single CO-MRSA clonal type, ST30:Z, accounted for 41.0% (an estimated 330 cases) of the total number of CO-MRSA infections above the baseline level (figure 2A). In contrast, only an estimated 50 NO-MRSA and 9 LTCF-MRSA infections caused by ST30:Z were noted during the 7-year study period (figures 2B and 2C). The majority (81.7%) of ST30:Z isolates were recovered from SSTIs. Notably, this clonal type was not frequently recovered from worldwide collections and has only been implicated in an outbreak among Polynesians in Australia in 1998 [24, 36].

The 4 predominant CO-MRSA clonal types accounted for 43.6% of the total number of NO-MRSA infections and 13.7% of the total number of LTCF-MRSA infections (figure 3). However, the number of NO-MRSA infections (n = 200) associated with these 4 clonal types was significantly lower than the number of CO-MRSA infections (n = 927), which suggests an increased capacity for community spread. Although not statistically significant, ST8:S and ST30:Z isolates were more likely to be MDR when they were recovered from NO-MRSA than when they were recovered from CO-MRSA infections (27.3% vs. 11.8% [P = .42] and 10.2% vs. 1.5% [P = .05], respectively). This suggests that common antibiotic usage in the hos-
Figure 3. Association of clonal types with disease onset characteristics. The weighted percentage of isolates within each clonal type (designated by multilocus sequence typing, pulsed-field gel electrophoresis, and staphylococcal chromosomal cassette mec type) was presented according to disease onset characteristics: community onset (CO) with no prior health care exposure, CO with prior outpatient exposure, CO with prior hospitalization, nosocomial (NO), and long-term-care facility (LTCF) onset.

Predominant NO-MRSA genotypes. Two clonal types, ST36:A and ST5:D, were strongly associated with NO-MRSA and LTCF-MRSA infection (figure 3). The majority of isolates belonging to these clonal types carried the type II SCCmec, and >90% of these isolates were MDR. ST36:A belongs to ST36 complex, an epidemic clonal type (EMRSA-16) in hospitals in the United Kingdom [33, 37]. It accounted for 10.2% of NO-MRSA and 8.1% of LTCF-MRSA infections in the present study (figure 3). Among cases of CO-MRSA infection, ST36:A was recovered from an estimated 38 patients (2.9%), all of whom had been hospitalized within the preceding 2 years.

ST5:D belongs to the ST5 clonal complex, a pandemic hospital MRSA clonal type that is frequently referred to as the “New York/Japan” clone [33, 38]. This clonal type was associated with 34.1% of the total number of NO-MRSA infections and 66.9% of the total number of LTCF-MRSA infections (figure 3). Although ST5:D was recovered from 133 cases of CO-MRSA infection, 77.5% of these were from patients who had been hospitalized at SFGH within the preceding 2 years (figure 3). Importantly, a subtype of this strain, designated ST5:Ds, emerged in 2001 and accounted for an estimated 158 cases in 2001–2002: 78 NO-MRSA, 43 CO-MRSA, and 38 LTCF-MRSA (figure 2). A case-control study identified a higher frequency of ventilator-associated pneumonia, postoperative wound infections, and catheter-associated infections among the ST5:Ds outbreak subtype, compared with concurrent MRSA control isolates [32]. Although most ST5:D isolates carried the type II SCCmec element and were MDR, an estimated 46 ST5:D MRSA isolates were not MDR and carried the type IV SCCmec element (table 1). The majority (71.7%) of these were recovered from CO-MRSA isolates. Thus, it appears that isolates bearing the type IV SCCmec were capable of spreading in the community, whereas type II isolates were largely restricted to the hospital.

DISCUSSION

The present study has underscored the usefulness of molecular genotyping methods for defining community-adapted MRSA strains. Epidemiologic definitions based on time after hospital admission, lack of recent health care use, or other health care–associated risk factors may underestimate the extent of the community MRSA reservoir. In San Francisco, 4 MRSA clonal types (ST8:C, ST8:S, ST59:P, and ST30:Z) were associated with the dramatic ascent in community methicillin resistance between 1998 and 2002. The vast majority (90.6%) of CO-MRSA infections associated with these 4 clonal types originated from patients who had a history of hospitalization or outpatient services. However, it does not necessarily follow that the patients became colonized as a result of their hospital visits or that feral hospital isolates caused their subsequent disease onset.
in the community. If these MRSA isolates are feral hospital-endemic isolates, they would be expected to cause significantly greater numbers of hospital-onset than community-onset infections. We found, to the contrary, however, that the preponderance of cases associated with these 4 clonal types were attributable to community onset, as opposed to hospital or LTCF onset (76.9% vs. 19.4% vs. 3.7%; P = .0005) (figure 3). Furthermore, on the basis of its temporal distribution, at least 1 clonal type, ST8:S, became established in the local community and spread from there to the hospital and LTCF.

There is additional corroborative evidence for a community reservoir of these 4 clonal types. In a previous study of incarcerated patients in San Francisco county jails, these 4 clonal types were associated with most of the SSTIs [10]. A community reservoir of ST59:P, ST8:C, and ST30:Z was identified among injection drug users in 1999 [17], 1 year before the emergence of ST8:S in San Francisco. In 2000, 61 of 64 consecutive walk-in patients who received surgical treatment for SSTIs at the hospital-based outpatient ISIS clinic had MRSA isolates that belonged to these 4 clonal types; the first ST8:S in San Francisco was identified at this clinic in September 2000 [11].

These community-adapted MRSA isolates have intrinsic features that may facilitate their spread in the community. First, the fitness cost of antibiotic resistance may be minimized by carriage of the smaller type IV SCCmec element (21–24 kb); this element, unlike the larger types I, II, and III SCCmec elements, encodes for no resistance determinants other than for β-lactams [19, 20]. Thus, only 6.7% of these 4 clonal types are MDR. Second, 2 of these clonal types, ST8:S and ST30:Z, also carry the PVL genes [11]. PVL is a bicomponent cytotoxin virulence factor that is associated with SSTIs, as well as with severe necrotizing pneumonia [21–23, 39]. Additional studies investigating the role of other exotoxins associated with CO-MRSA [16, 23, 40, 41] are currently under way.

The majority (73.8%) of cases associated with ST5:D and ST36:A had hospital and LTCF onset. These isolates were MDR and contained type II SCCmec. This is in accord with the accepted view that their reservoir is the hospital [33, 37, 38]. In contrast, the type IV SCCmec–bearing ST5:D isolates are multidrug sensitive and primarily associated with CO-MRSA infections. Their low prevalence in the hospital supports the view that their reservoir is the hospital [33, 37, 38]. The spread of community-adapted MRSA strains into the hospital not only increases the frequency of methicillin-resistant strains in this setting but also may select for MDR strains with enhanced capacity for community transmission. Changes in the frequency of multidrug resistance are currently under active surveillance. The empirical use of β-lactams for community-onset staphylococcal infections is no longer prudent and requires microbiologic culture and antimicrobial susceptibility testing to guide treatment.

References


