

## Trends in Prescribing $\beta$ -Lactam Antibiotics for Treatment of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Infections<sup>∇</sup>

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Rates of prescribing of  $\beta$ -lactam antibiotics as initial empirical therapy for patients with skin and soft tissue infections (SSTIs) caused by molecularly and epidemiologically characterized community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) isolates were assessed over a 3-year period. A prospectively developed database was used to calculate the prevalence of CA-MRSA SSTIs from 2004 to 2006. Molecular characterization of the MRSA isolate and medical record review for assessment of initial antimicrobial therapy were performed on a subset of patients. Among 2,636 patients with *S. aureus* SSTIs, the prevalence of CA-MRSA was 9% in 2004, 16% in 2005, and 21% in 2006 ( $P < 0.0001$ , chi-square test for trend). Seventy-five percent of CA-MRSA isolates tested were of the USA 300 or 400 clone type. Ninety-two percent of CA-MRSA isolates tested were positive for Panton-Valentine leukocidin, of which 90% carried staphylococcal chromosomal cassette *mec* type IV. The rate of use of a  $\beta$ -lactam antibiotic as initial empirical therapy for patients with CA-MRSA SSTIs was 86%, 77%, and 60% in 2004, 2005, and 2006, respectively ( $P = 0.04$ , chi-square test for trend). Thirty percent of  $\beta$ -lactam-treated patients had a documented risk factor for CA-MRSA infection. The use of a  $\beta$ -lactam antibiotic as initial empirical therapy for CA-MRSA SSTIs has decreased significantly over the past 3 years. However, even as the prevalence of CA-MRSA SSTIs approaches 25%, the majority of patients are still receiving inactive antimicrobial therapy. Further evaluation of the outcomes associated with discordant therapy for CA-MRSA SSTIs is needed.

Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) among patients without recent health-care exposures are increasingly being recognized (8, 10, 19, 23, 28). The primary clinical presentation is in the form of skin and soft tissue infections (SSTIs), but necrotizing pneumonia, endocarditis, bacteremia, central nervous system infections, osteomyelitis, and other invasive diseases have also been reported (4, 10, 11, 16, 19, 23). Community-associated MRSA (CA-MRSA) has been defined both epidemiologically (positive culture results within 48 to 72 h of hospital admission, no hospitalizations within the last year, and no history of MRSA colonization or infection) and molecularly (pulsed-field gel electrophoresis type USA 300 and 400) (7, 10, 18). CA-MRSA typically also has a characteristic antibiotic susceptibility pattern, carries specific virulence toxins such as the Panton-Valentine leukocidin (PVL), and possesses a specific staphylococcal chromosomal cassette (SCC*mec* type IV) (7, 18, 20, 24, 28).

The prevalence of CA-MRSA varies greatly by geographic area. A study from San Diego, CA, noted a 65% CA-MRSA rate over a 15-year period while other regions have reported much lower rates, ranging from 4% to 50% (2, 19, 20, 28). An

appreciation of local CA-MRSA rates is critical to the appropriate prescribing of empirical antimicrobial therapy (7).

Guidelines have suggested that alternatives to  $\beta$ -lactam antibiotics be used as empirical therapy for patients presenting with SSTIs in areas where the prevalence of CA-MRSA exceeds 10 to 15% (7). An accurate calculation of CA-MRSA rates requires coordination of data from clinicians, microbiology laboratories, and hospital epidemiologists, a system that is not usually available or easily implemented. Thus, clinicians usually rely on individual patient characteristics described in the literature as being associated with CA-MRSA. Appreciation of these risk factors and their incorporation into clinical practice are an evolving process that is likely to improve over time. In the interim, however,  $\beta$ -lactam antibiotics continue to be prescribed empirically to a proportion of patients who have an infection with CA-MRSA (22, 25, 28). Although some studies have found that the use of an inactive antimicrobial regimen for CA-MRSA infection is not necessarily associated with adverse outcomes, more-recent data suggest that there is a difference in clinical cure rates based on adequacy of the antibiotic prescribed (3, 5, 12, 17, 18, 22).

To our knowledge, no study to date has reported trends over a 3-year period in treatment for MRSA infections that are well characterized both molecularly and epidemiologically as being caused by community-associated strains. The purpose of this study was to assess the prevalence and molecular epidemiology of CA-MRSA at Yale-New Haven Hospital (YNHH) and evaluate changes in prescribing patterns over a 3-year period.

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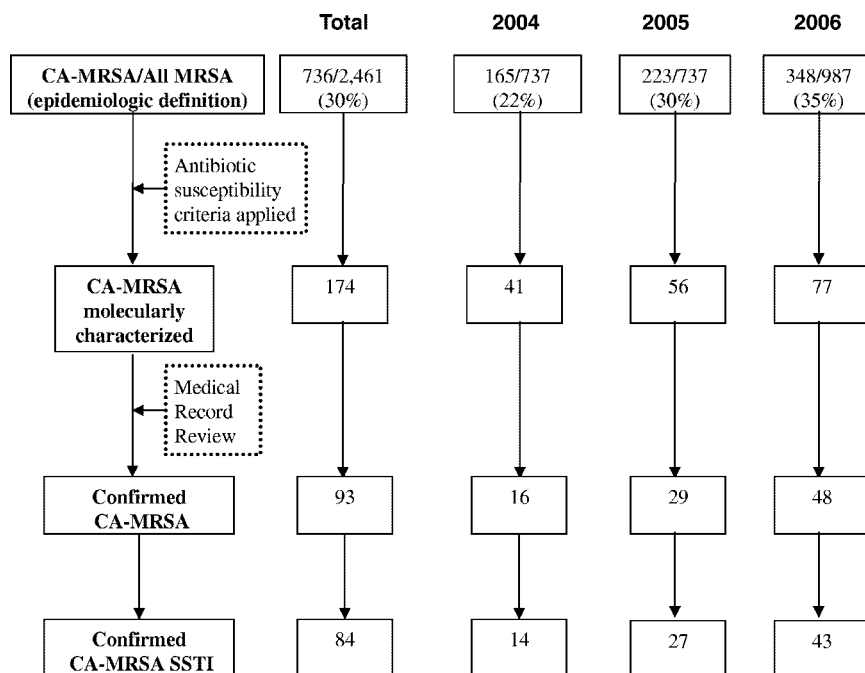


FIG. 1. Flow diagram of chart-confirmed CA-MRSA SSTI study population from 2,461 unique MRSA patients.

#### MATERIALS AND METHODS

**Study population.** YNH is a 944-bed academically affiliated medical center providing primary and tertiary care to residents of the New Haven area and southern Connecticut. In 2006, there were 50,369 hospital discharges and 503,656 outpatient visits, including 113,921 emergency room visits. The YNH Clinical Microbiology Laboratory receives specimens from inpatients, hospital-affiliated outpatient clinics, and the emergency room. As part of the MRSA Surveillance Program of the YNH Department of Quality Improvement Support Services, all patients with a clinical or surveillance culture positive for MRSA are prospectively entered into a database by an infection control practitioner and the isolate is banked by the Epidemiology Laboratory. From this database, we obtained information which was routinely recorded for each patient, including the date and site of culture, duration of hospitalization, and previous MRSA history. Separate hospital databases provided information as to whether a patient had been hospitalized at YNH in the prior year and on the total number of patients with SSTIs (infection of skin, wound, or abscess) due to any *S. aureus* isolate (including both methicillin susceptible and resistant) by study year.

**Selection of patients and outcome definitions.** The patients eligible for inclusion in this study had a culture positive for MRSA at YNH between 1 January 2004 and 31 December 2006 and met the epidemiological definition of CA-MRSA, including having the MRSA culture obtained within 48 h of hospital admission, no hospitalizations within the last year, and no history of MRSA colonization or infection. Patients who did not meet this epidemiologic definition were excluded. Duplicate isolates and surveillance cultures were also excluded. Patients with a culture obtained from a wound or abscess were defined as having an SSTI. The prevalence of CA-MRSA SSTIs was calculated by dividing the number of patients with SSTIs due to CA-MRSA by the number of patients with any *S. aureus* SSTI (including both methicillin-susceptible and -resistant isolate infections).

Patients eligible for the medical record review and molecular testing portion of the study had to meet the above epidemiological criteria for CA-MRSA and also have an isolate with a susceptibility pattern suggestive of a USA 300 or 400 strain. Specifically, the MRSA isolate had to be sensitive to trimethoprim-sulfamethoxazole, rifampin, gentamicin, clindamycin, and vancomycin. Because clindamycin susceptibility data were not uniformly available in 2006, a random sample of CA-MRSA isolates was selected via a random number generator from each month and tested. Isolates susceptible to clindamycin and meeting the other antimicrobial susceptibility criteria were included in the study.

**Laboratory methods.** MRSA isolates were identified by disk diffusion criteria defined by the Clinical and Laboratory Standards Institute. The presence of the

*lukF* and *lukS* genes encoding PVL and the staphylococcal chromosome cassette *mec* (SCC*mec*) type were assessed using previously described PCR methods (13, 21). Isolates also underwent typing by pulsed-field gel electrophoresis (PFGE) using the restriction enzyme *Sma*I, as previously described, with controls for USA 100 to 800 PFGE types provided by the Network on Antimicrobial Resistance in *Staphylococcus aureus* supported under NIAID/NIH contract no. N01-AI-95359 (1, 26). Interpretation of laboratory results was performed prior to and without knowledge of the results of the medical record review.

**Medical record review.** Medical records were reviewed for the following information: (i) verification of community-associated epidemiology as recorded in the database (with cases reclassified as health-care-associated infections if there was evidence of surgery, admission to another hospital, or residence in a non-hospital health-care facility in the last year), (ii) identification of putative risk factors for CA-MRSA (having a history of contact sports, incarceration, military duty, illicit drug use, homelessness, or day-care attendance or having family members with MRSA or similar skin infections), (iii) initial antimicrobial agent prescribed, and (iv) whether incision and drainage were performed. This study was approved by the Institutional Review Board of Yale University School of Medicine.

**Statistical methods.** Data were analyzed using EPI Info software (version 3.3.2; CDC). Categorical variables were tested using the chi-square test or Fisher's exact test. Trends over the study period were evaluated with the chi-square test for trend.

#### RESULTS

**Prevalence of CA-MRSA SSTIs.** In the 3-year study period, a total of 2,461 unique patients with a culture positive for MRSA were identified. The proportion of patients meeting our epidemiological definition of having a CA-MRSA infection increased from 165 (22%) to 223 (30%) to 348 (35%) over the 3-year period (Fig. 1). SSTIs were the predominant infections caused by CA-MRSA and accounted for 67 (41%), 123 (55%), and 238 (68%) of the CA-MRSA infections in 2004, 2005, and 2006, respectively ( $P < 0.01$ , chi-square test for trend). Among the 2,636 unique patients identified as having an *S. aureus* SSTI (including both methicillin-sensitive and

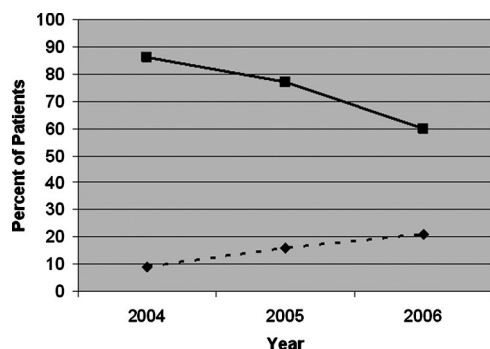


FIG. 2. The proportion of patients with a CA-MRSA SSTI being prescribed a  $\beta$ -lactam (solid line) decreased from 2004 to 2006 ( $P = 0.04$ , chi-square test for trend) as the prevalence of CA-MRSA SSTIs (dashed line) increased over the same time period ( $P < 0.0001$ , chi-square test for trend).

-resistant isolate infections) at YNH in the 3-year period, the prevalence of CA-MRSA SSTIs was 67/737 (9%) in 2004, 123/782 (16%) in 2005, and 238/1117 (21%) in 2006 ( $P < 0.0001$ , chi-square test for trend) (Fig. 2).

**Molecular epidemiology of CA-MRSA.** From the total group of CA-MRSA isolates meeting our epidemiological criteria for community-associated infection, we identified 183 that also met the antimicrobial susceptibility criteria. Nine isolates were not stored and thus were not available for further testing. The remaining 174 isolates (95%) were available for molecular evaluation (Fig. 1).

The molecular characteristics of the MRSA isolates from patients confirmed to have community-associated infection by medical record review are shown in Table 1. Strains consistent with the USA 300 clone type were identified in each year studied and accounted for 38%, 83%, and 69% of all chart-confirmed CA-MRSA isolates in 2004, 2005, and 2006, respectively. The USA 400 clone type was much less frequent but nevertheless present in each year. The only other clone type identified was USA 100 (one or two strains per year; Table 1). In addition, there were a small number of strains in each year that could not be classified as a USA 100 to 800 type. Of this group, there was no prevalent pattern identified, although similarities to the published PFGE pattern of the USA 1000 type were noted (27). No control for USA 1000 type was available for confirmatory testing at the time of the study.

The proportion of confirmed CA-MRSA strains positive for PVL was 92% over the 3-year period (Table 1). Among the six

TABLE 2. Characteristics of study patients with a chart-confirmed CA-MRSA SSTI

Characteristic	No. of patients positive (%)			
	Total ( <i>n</i> = 84)	2004 ( <i>n</i> = 14)	2005 ( <i>n</i> = 27)	2006 ( <i>n</i> = 43)
Age (yr)				
0–10	13 (15)	2	3	8
11–20	19 (23)	4	5	10
21–50	41 (49)	5	13	23
>50	11 (13)	3	6	2
Male	55 (66)	9 (64)	20 (74)	26 (60)
Hospitalized <sup>a</sup>	39 (46)	11 (79)	8 (30)	20 (47)
$\beta$ -Lactam therapy <sup>b</sup>	57 (70) <sup>c</sup>	12 (86)	20 (77)	25 (60)
Risk factor for CA-MRSA <sup>d</sup>	17 (30)	4 (33)	6 (30)	7 (28)

<sup>a</sup> Cultures were obtained at the time of admission or less than 48 h after admission.

<sup>b</sup>  $P = 0.04$ , chi-square test for trend for decrease over the 3-year study period.

<sup>c</sup> Data not available for two patients.

<sup>d</sup> Among those receiving  $\beta$ -lactams.

PVL-negative strains, three were of the USA 100 type, one was a USA 300 strain, and the remaining two isolates could not be classified as a USA 100 to 800 strain. Fourteen confirmed CA-MRSA strains were not available for evaluation of PVL. Among PVL-positive strains, 90% were found to carry SCCmec type IV.

Forty-four patients initially designated as having a community-associated infection by epidemiological criteria were reclassified as having a health-care-related MRSA infection after medical record review (further detailed below). Nine of these patients (20%) had a USA 300 clone type compared to 63 (68%) of the 93 patients who were confirmed by record review to have a community-associated infection. Thus, patients with a CA-MRSA infection were eightfold more likely than patients with a health-care-associated MRSA infection to have a USA 300 clone type (odds ratio, 8.2 [95% confidence interval, 3.3 to 21.0];  $P < 0.0001$ ). There were no USA 400 strains found among patients with health-care-associated MRSA.

**Empirical antimicrobial use.** Medical records were requested on all 174 patients whose isolates were molecularly tested. One hundred forty-eight (85%) were available for review and contained information on the visit date of interest. The remaining charts either were not retrievable from the file room or did not contain information about the relevant visit. Of the total group reviewed, 44 (30%) were reclassified as health-care-associated MRSA infections due to documentation of prior hospitalization, residence in a long-term health-care setting, or a surgical procedure (inpatient and/or outpatient) within the last year. An additional 11 (7%) patients were excluded from further analysis as their isolates were designated as representing colonization rather than infection by the primary providers and no specific therapy was provided.

There were only nine infections due to CA-MRSA that were not categorized as an SSTI in the 3-year study period (two urinary tract infections, one bacteremia case, one sinusitis case, and five pneumonia cases). The remaining 84 infections were categorized as SSTIs (i.e., skin, wound, or abscess) and were the focus of the antimicrobial management analyses. As shown in Table 2, more than half of the patients meeting our defini-

TABLE 1. Molecular characteristics of chart-confirmed CA-MRSA isolates

Characteristic	No. of isolates positive/total no. (%)			
	2004	2005	2006	Total
PVL	15/16 (94)	28/29 (97)	30/34 <sup>a</sup> (88)	73/79 (92)
SCCmec type IV	11/15 (73)	28/28 (100)	27/30 (90)	66/73 (90)
USA 100 clone	2/16 (13)	1/29 (4)	2/48 (4)	5/93 (5)
USA 300 clone	6/16 (38)	24/29 (83)	33/48 (69)	63/93 (68)
USA 400 clone	2/16 (13)	2/29 (7)	2/48 (4)	6/93 (7)
Non-USA 100 to 800	6/16 (38)	2/29 (7)	11/48 (23)	19/93 (20)

<sup>a</sup> The PVL assay was performed on 34 of 48 isolates confirmed as CA-MRSA in 2006.

tion of having a CA-MRSA SSTI were 10 to 50 years of age in each year studied. There was a greater proportion of males than of females identified with CA-MRSA in each year. Approximately half the patients were hospitalized for treatment of their infection.

The rate of utilization of a  $\beta$ -lactam antibiotic as initial empirical therapy for SSTIs due to CA-MRSA decreased from 86% to 77% to 60% over the years 2004, 2005, and 2006, respectively ( $P = 0.04$ , chi-square test for trend) (Table 2). As shown in Fig. 2, this decrease was in inverse relationship to the statistically significant increasing prevalence of CA-MRSA SSTIs. Patients were almost threefold less likely to receive a  $\beta$ -lactam antibiotic for a CA-MRSA SSTI in 2006 than in 2004 and 2005 (odds ratio, 0.37;  $P = 0.04$ ), the same period in which the prevalence of CA-MRSA SSTIs more than doubled.

A putative epidemiological risk factor for CA-MRSA infection was identified in 30% of patients who were treated with a  $\beta$ -lactam as initial empirical therapy. Specifically, the percentage of patients prescribed a  $\beta$ -lactam who had a risk factor for CA-MRSA were 33% in 2004, 30% in 2005, and 28% in 2006 (Table 2). The majority of patients with SSTIs (67/84, 80%) underwent incision and drainage regardless of antimicrobial therapy.

## DISCUSSION

To our knowledge, this is one of the first studies to evaluate prescribing trends over a 3-year period for infections that are well characterized epidemiologically, clinically, and molecularly as being due to CA-MRSA. Such data are critically important in assisting clinicians to optimize the accuracy of empirical prescribing that is integral to treating these acute infections.

The overall rate of CA-MRSA in the YNH catchment area was moderately high (>30%) and increased over the 3-year study period. The proportion of patients with SSTIs due to CA-MRSA compared to methicillin-susceptible *S. aureus* or health-care-associated MRSA also increased significantly, from 9% in 2004 to 21% in 2006. An important finding in our study is that empirical  $\beta$ -lactam use for CA-MRSA SSTIs decreased significantly over this same 3-year period, suggesting that clinicians are recognizing this emerging infection and modifying their treatment approach as recommended by CDC guidelines (7).

However, despite this decrease, nearly 60% of patients presenting with CA-MRSA SSTIs still received  $\beta$ -lactams as initial empirical therapy in 2006. A similar rate of  $\beta$ -lactam use was found among patients treated in 2004 for MRSA SSTIs in 11 emergency rooms throughout the United States (18). Recently, a study from a community-based clinic in Boston, MA, found that the majority of patients with SSTIs were no longer being prescribed a  $\beta$ -lactam in 2005 (25). The study differed from ours in that molecular characterization of the strains was not performed and approximately one-quarter of patients had a known previous MRSA infection, decreasing the likelihood of  $\beta$ -lactam utilization and distinguishing the study population from ours, in which there was no known history of MRSA. Another important difference is that more than half of the Boston clinic population were men who have sex with men, an exposure that has been associated with increased CA-MRSA

risk (14, 25). It may be that smaller clinical sites serving higher-risk populations have more rapidly and uniformly modified their approach to empirical therapy of SSTI.

About one-third of the patients in our study had one or more of the factors that have been associated with CA-MRSA, including young age, contact sports, incarceration, illicit drug use, homelessness, and day-care attendance (6, 9, 29). As reported in previous studies, specific risk factor profiles cannot reliably help clinicians distinguish between CA-MRSA and methicillin-susceptible isolate infections (15). Thus, knowledge of local prevalence rates is still critical to appropriate empirical prescribing.

Initial classification of our isolates as community associated was performed via a computerized database. Of the subset of patients whose charts were reviewed, only 63% of isolates could be confirmed as community-associated infections by epidemiologic criteria. Prior hospitalization in outside community hospitals, recent outpatient surgical procedures, and residence in long-term care facilities were the main factors that resulted in reclassification of MRSA isolates as health care associated. These variables are rarely available in automated electronic databases, suggesting that studies relying on such databases for identification of CA-MRSA may be hindered by misclassification bias. Interestingly, the utilization of molecular characteristics was very helpful in identifying the isolates that ultimately met our strict definition for being CA-MRSA. The availability of more-rapid methods for typing makes it feasible to use molecular features to further define CA-MRSA when traditional chart review or direct patient interview is not possible (27).

The main limitation of our study is the use of chart abstraction for assessment of antimicrobial regimens and risk factors. The utilization of an active, prospectively developed, surveillance database helps to minimize some of the issues of a retrospective study design. Since we cannot assume that the risk factors of interest were uniformly recorded, we limited this part of the analysis to being primarily descriptive. In addition, the unavailability of complete clindamycin susceptibility data in 2006 could have influenced the number of patients selected for medical record review in that year. For this reason, we do not base any of our results on antimicrobial susceptibility criteria alone and used the information only to further identify patients for chart review and molecular characterization of their isolates. Finally, the generalizability of our findings may be limited as the study population was from one hospital, although the catchment area includes both rural and urban settings.

To our knowledge, our study is the first to synthesize epidemiologic, clinical, and molecular typing criteria to identify annual trends in empirical  $\beta$ -lactam therapy for CA-MRSA SSTIs. The prevalence of CA-MRSA SSTIs has increased significantly and is approaching 25%. Although the use of a  $\beta$ -lactam as initial empirical therapy has decreased significantly over the past 3 years, more than half of patients presenting with CA-MRSA SSTIs are still receiving inactive antimicrobial therapy. The findings emphasize the need for individual institutions to identify their CA-MRSA prevalence rates, as this may help optimize empirical antimicrobial choice. Further study of the role of empirical antimicrobial use in outcomes in



patients with CA-MRSA SSTIs is warranted, particularly in light of the high frequency of  $\beta$ -lactam use that currently exists.

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