

# Population-Based Incidence and Characteristics of Community-Onset *Staphylococcus aureus* Infections with Bacteremia in 4 Metropolitan Connecticut Areas, 1998

Craig A. Morin<sup>1,a</sup> and James L. Hadler<sup>2</sup>

<sup>1</sup>Epidemiology Program and <sup>2</sup>Infectious Diseases Division,  
Connecticut Department of Public Health, Hartford

This study retrospectively analyzed the magnitude and epidemiology of community-onset *Staphylococcus aureus* (COSA) infections and methicillin-resistant *S. aureus* (MRSA) infections in 4 Connecticut metropolitan areas (population, 1.1 million). The study looked at hospital medical records of persons admitted with *S. aureus* bacteremia in 1998. COSA was categorized as "health care associated," "with underlying medical condition," or "no underlying medical condition." Overall, 48% of *S. aureus* bacteremic infections were COSA (incidence, 17 cases/100,000 persons). Incidence increased with age and higher population density. In all, 62% of infections were health care associated; 85% of the remaining cases had underlying medical conditions. MRSA accounted for 16% of health care-associated cases and cases with underlying conditions but no cases with no underlying conditions. COSA bacteremic infections are as common as those due to pneumococci. MRSA is a well-established cause of COSA among persons at high medical risk for *S. aureus* infection. Additional study to understand community-onset MRSA acquisition is needed.

Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have become increasingly common over the last several decades and are now present or endemic in most US hospitals [1]. Initially, the focus of concern about MRSA was the hospital setting; the occurrence and epidemiology of community-acquired infections were recognized and reported only infrequently [2, 3]. More recently, an increasing proportion of MRSA isolates are from hospitalized patients admitted from the community [4–8]. The growing concern that MRSA is emerging as a community pathogen is leading to further examination of the epidemiology of community-acquired *S. aureus*. Much uncertainty exists regarding the epidemiology of *S. aureus* acquisition in the community and the extent to which MRSA has become established [9–12]. Understanding the epidemiology of MRSA infection in the community setting has important implications for future efforts to control the emergence of glycopeptide-resistant staphylococci. If hospital-generated MRSA has become a community pathogen, then a similar pattern of spread might be expected for vancomycin-intermediate and -resistant *S. aureus* in the absence of higher

levels of control. We believe that population-based surveillance is a useful means to better define the epidemiology of *S. aureus* in community settings. Thus, as a special project of the Connecticut Emerging Infections Program, we set out to determine the epidemiology of community-onset *S. aureus* (COSA) bloodstream infections and the extent to which they are caused by MRSA in 4 distinct areas of Connecticut representing 41 Connecticut communities.

## Methods

**Study population.** Four Connecticut metropolitan areas comprising 41 towns with a total population of 1,124,337 (1998 Connecticut population estimates) and 9 acute-care hospitals were selected for study. These metropolitan areas were selected because they had central towns with major acute-care hospitals, surrounding towns with health care patterns, such that >90% of all persons needing hospitalization with acute, severe invasive bacterial disease caused by group A streptococcus or *Streptococcus pneumoniae* were hospitalized in one of the central town hospitals, and hospital laboratories that agreed to participate in the study (Connecticut Department of Public Health, unpublished data). The areas were New Haven (9 towns; population, 311,331), Stamford (7 towns; population, 305,881), Waterbury (11 towns; population, 254,324), and New London (14 towns; population, 252,801). Persons eligible for inclusion were residents of towns in the respective metropolitan area and were hospitalized at one of the central town hospitals with acute COSA bloodstream infection in 1998.

**Study design.** Retrospective case ascertainment was initiated within the 9 metropolitan area hospitals that provide health care services to residents of the metropolitan surveillance areas. The hospital clinical microbiology laboratories maintain records of all *S. aureus* isolates. Microbiology directors were asked to submit com-

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<sup>a</sup> Present affiliation: Acute Disease Epidemiology Section, Minnesota Department of Health, Minneapolis.

Reprints or correspondence: Dr. James Hadler, Infectious Diseases Division, Connecticut Dept. of Public Health, 410 Capitol Ave., MS 11-FDS, PO Box 340308, Hartford, CT 06134-0308 (james.hadler@po.state.ct.us).

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puter-generated microbiology reports, which were used to identify *S. aureus* bloodstream infections for the 12 months from 1 January 1998 through December 1998. For persons with >1 *S. aureus* bloodstream isolate, only the first isolate was counted. Medical records of hospitalized patients were reviewed, and information was abstracted on a standardized data collection form. Abstracted information included town of residence, age, sex, race/ethnicity, date of admission, date of discharge, date of culture collection, outcome (died, discharged home, or discharged to another care facility), infection sites, antibiotic susceptibility testing results, history of hospitalization in the past year, iatrogenic risk factors for staphylococcal bacteremia (peritoneal or hemodialysis, indwelling device at home before admission), and underlying illnesses (vascular disease, splenectomy/asplenia, immunoglobulin deficiency, renal failure, human immunodeficiency virus [HIV]/AIDS, congestive heart failure, acute varicella, systematic lupus erythematosus, organ transplant, solid organ and hematologic cancer, immunosuppressive therapy, asthma, alcohol abuse, injection drug use, blunt and penetrating trauma, sickle cell anemia, emphysema, chronic obstructive pulmonary disease, cirrhosis, burns, diabetes mellitus, atherosclerotic cardiovascular disease, and other underlying illness).

**Definitions.** From the information in the medical record, persons were classified as having "hospital-onset" or "community-onset" infection. A person with a hospital-onset infection was defined as a resident of the surveillance area with a first positive blood culture collected >2 days after hospital admission. Long-term care facilities were considered to be hospitals, and persons admitted from them were classified as having hospital-onset infections. A person with a community-onset infection was defined as a resident of the surveillance area with a first positive blood culture collected no later than 2 days after hospital admission who was hospitalized with a clinical illness consistent with an *S. aureus* infection. Patients were excluded from the study if they lived in towns outside the surveillance area, if their infection was determined to be a relapse of a past *S. aureus* infection, or if their positive blood culture was considered by the attending physician to be a contaminant and no antibiotic therapy was administered in response to the finding of a positive *S. aureus* blood culture.

Community-onset infections were further classified into 3 mutually exclusive categories: "health care associated," "with underlying medical condition," and "no underlying medical condition." Patients with community-onset infections were classified as having a health care-associated infection if the patient had a documented hospitalization within the 12 months before the collection date of the current positive blood culture, had undergone peritoneal or hemodialysis within the 12 months before the infection, or had an indwelling bladder or vascular device at home immediately before hospital admission for the current infection. Community-onset infections were defined as "with underlying medical condition" if the patient had a chronic underlying medical condition that may have caused increased susceptibility to infection but no hospital documentation of any of the conditions that would have indicated the infection was health care associated. Community-onset infections were defined as no underlying medical conditions if the patient had no documented chronic underlying condition and did not qualify for the health care-associated category.

For analysis purposes, each of the 41 towns in the 4 metropolitan areas was classified and then regrouped as urban, mixed urban-

suburban, suburban, and rural, depending on the population density per square mile (urban,  $\geq 5000$ ; mixed urban-suburban, 2500–4999; suburban, 1000–2499; and rural,  $<1000$ ) [13].

***S. pneumoniae* and group A streptococcus data.** Data on the incidence of community-onset bacteremic infections with *S. pneumoniae* and group A streptococcus were obtained from the Connecticut Emerging Infections Program Active Bacterial Core Surveillance project. Methods for active laboratory surveillance for this project have been described elsewhere [14].

**Statistical methods.** Simple descriptive epidemiological analyses, contingency tables and 95% confidence intervals (CIs), and  $\chi^2$  test for linear trend were generated by use of Epi Info version 6.04b software [15].

## Results

In total, 634 persons in the study areas had *S. aureus* bacteremia in 1998. Medical records were available for 621 (98%) patients. Of these patients, 457 (73%) resided within 1 of the 41 towns within the surveillance area, and 402 (88%) had definite *S. aureus* bacteremia. Of the 402 *S. aureus* bacteremic infections, 201 were hospital onset, including 55 from long-term care facilities; 9 (2%) had a relapse of a previous infection or were transferred from a hospital outside the surveillance area; and 192 (48%) had onset of disease in their community. These 192 patients constituted the final study population of community-onset bacteremic infections.

**Incidence of community-onset infection.** The overall incidence of COSA bloodstream infection was 17 cases/100,000 persons. The highest incidences were among males, 20.9 cases/100,000 persons (range, 15.5–29.8 cases by surveillance area); adults  $\geq 65$  years old, 52 cases/100,000 persons (range, 44.3–57.8 cases); blacks, 40.3 cases/100,000 persons (range, 22.1–51.7 cases); and residents of urban areas, 36.8 cases/100,000 persons (table 1). Risk steadily increased with increasing age and with increasing population density (table 1). These increasing risks were present in each of the 4 surveillance areas and for each category of COSA (health care associated, with and without underlying medical conditions) when analyzed separately. There was no seasonality in the occurrence of COSA bacteremic infections, nor were children  $\leq 2$  years old more likely to be affected than children  $\leq 15$  years old.

Twenty-nine (15%) patients had MRSA infections. The incidence of community-onset MRSA bacteremic infection was 2.5 cases per 100,000 persons. There were no statistically significant ( $P < .05$ ) differences when we compared the percentages of all cases that were MRSA by sex, age group, race/ethnicity, or population density; however, residents of the Waterbury metropolitan area were significantly more likely than residents of the other surveillance areas to have had MRSA (30% vs. 11%, respectively;  $P < .01$ ,  $\chi^2$  test). This difference was consistent for all sex, age, and race/ethnic groups and for both the health care-associated group and the group with underlying medical conditions.

**Table 1.** Rate of community-onset *Staphylococcus aureus* (COSA) bloodstream infection by selected demographic characteristics in 4 Connecticut metropolitan areas, 1998.

Characteristic	COSA/ 100,000 persons <sup>a</sup>	RR (95% CI)	P
Sex			
Female	13.4	Ref (—)	
Male	20.9	1.6 (1.2–2.1)	.002
Age range, years			
<15	2.3	Ref	
15–24	2.4	1.0	
25–34	6.7	2.8	
35–44	17.1	7.2	
45–65	26.63	11.8	
≥65	52.0	21.9	<.0001 <sup>b</sup>
Race/ethnicity			
White	13.8	Ref (—)	
Hispanic	16.0	1.2 (0.7–1.9)	
Black	40.3	2.9 (2.1–4.1)	.002
Season (quarter of year)			
January–March	17.5	Ref (—)	
April–June	17.8	1.0 (0.7–1.4)	
July–September	18.2	1.0 (0.7–1.5)	
October–December	15.0	0.9 (0.6–1.2)	NS
Metropolitan area			
New London	12.2	Ref (—)	
Stamford	12.3	1.0 (0.6–1.6)	
Waterbury	15.8	1.2 (0.7–2.1)	
New Haven	24.5	2.0 (1.3–3.0)	.0001
Population density			
Rural	10.7	Ref	
Suburban	11.3	1.1	
Mixed urban-suburban	20.1	1.9	
Urban	36.8	3.4	<.00001 <sup>b</sup>

NOTE. CI, confidence interval; NS, not significant; Ref, reference; RR, relative risk.

<sup>a</sup> Based on 1990 US census data.

<sup>b</sup>  $\chi^2$  test for linear trend.

When compared with incidence rates among other bacterial bacteremic community-onset infections under similar surveillance in Connecticut, COSA infections were nearly as common as those due to *S. pneumoniae* (17.0 vs. 21.2 cases/100,000 persons), and the rate of community-onset MRSA infection (2.5 cases/100,000 persons) was the same as that for group A streptococcus (table 2).

**Categorization of community-onset infections.** A key outcome of this study was whether patients with COSA bacteremia might have acquired a staphylococcal strain as a result of contact with the health care system or in the community. The majority (62%) of infections, including the majority with MRSA, were clearly health care system associated (table 3). Most (71%) in the health care-associated subgroup had been hospitalized in the preceding 12 months, and nearly half had an indwelling device at the time of admission.

Of the 38% without such clearly intense health care system contact, most (61 [85%] of 72) had at least 1 discernable underlying medical condition (table 3). The most common underlying conditions were diabetes mellitus (38%), cardiovascular disease (35%), injection drug use (28%), and HIV/AIDS (18%). Only a small minority (11 persons: 15% of all non-health

care-associated COSA and 6% of all COSA) had community-onset disease with no underlying medical conditions.

With 1 exception, there were no statistically significant demographic (see table 1) predictors of whether a COSA infection was health care associated or whether a non-health care-associated COSA infection had an underlying condition. Children <15 years old were less likely than persons in other age groups to have a health care-associated COSA infection (0/5 vs. 120/187;  $P < .01$ ). They also were less likely to have an underlying medical condition (1/5 vs. 60/67;  $P = .01$ ).

The most common clinically apparent sites of infection among the 120 patients with health care-associated bacteremia were indwelling device sites (35%), bacteremia without a focus (18%), cellulitis (17%), and endocarditis (13%). The most common clinical manifestations among the 61 patients with underlying medical conditions were bacteremia without a focus (26%), cellulitis (21%), endocarditis (18%), and pneumonia (16%). Most of the 11 patients without underlying conditions had deep tissue, soft tissue, or joint infections, including osteomyelitis (27%), abscesses (27%), and septic arthritis (18%).

The percentages of patients with MRSA among the health care-associated group and the group with underlying medical conditions were the same (16%). Among patients with each underlying condition, there were no notable differences in the percentages with MRSA. No patients with COSA with no underlying medical conditions had MRSA, although, given the small number of cases, this finding could have occurred by chance ( $P = .08$ , Fisher's exact 1-tailed test; table 3).

**Antibiotic resistance patterns.** Among the 192 COSA bloodstream infections, >75% of isolates were tested by the clinical laboratories for sensitivity to the following antibiotics: clindamycin, gentamicin, methicillin/oxacillin, penicillin, trimethoprim-sulfamethoxazole (TMP-SMZ), and vancomycin. Among MRSA isolates, most had multiple antibiotic resistance. Antibigrams revealed 59% were resistant to gentamicin, 59% to tetracycline, 57% to clindamycin, and 57% to TMP-SMZ. Among methicillin-sensitive isolates, 86% were resistant to penicillin, 8% to clindamycin, and 2% each to tetracycline, TMP-SMZ, and gentamicin. All isolates tested were susceptible to vancomycin. There were no significant differences between health care-associated and non-health care-associated COSA strains when antibiotic susceptibilities were compared for methicillin-resistant

**Table 2.** Incidence of community-onset bloodstream infections with *Staphylococcus aureus*, methicillin-resistant *S. aureus* (MRSA), *Streptococcus pneumoniae*, and group A streptococcus in 4 Connecticut metropolitan areas, 1998.

Community-onset bloodstream infection	No. of cases	Incidence/ 100,000 persons <sup>a</sup>
<i>S. aureus</i>	192	17.0
MRSA	29	2.5
<i>S. pneumoniae</i>	239	21.2
Group A streptococcus	29	2.5

<sup>a</sup> Based on 1990 US census data.

**Table 3.** Categorization of community-onset *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) bloodstream infections by health care and medical factors in 4 Connecticut metropolitan areas, 1998.

Category of infection	<i>n</i>	Total (in category), %	With MRSA, %
Total	192	100	15
Health care associated <sup>a</sup>	120	62	16
Hospitalized within prior 12 months	85	(71)	21
Indwelling line/catheter	59	(49)	7
Hemodialysis	38	(32)	5
Total not health care associated	72	38	14
≥1 Underlying medical condition <sup>a</sup>	61	(85)	16
Diabetes mellitus	23	(38)	13
Cardiovascular disease	19	(31)	21
History of injection drug use	17	(28)	12
Human immunodeficiency virus/AIDS	11	(18)	27
Other	37	(61)	11
No underlying medical conditions	11	(15)	0

<sup>a</sup> Patients may have had ≥1 health care or medical factor.

or methicillin-sensitive strains. Of note, no MRSA was resistant to methicillin alone.

**Consequences of COSA.** COSA bacteremic infections had substantial health care consequences and case-fatality rates. The median length of hospital stay for all infections was 11.0 days. The duration of hospitalization was highest among patients with underlying medical conditions (median, 16.5 days), followed by patients with no underlying medical conditions (median, 11.0 days) and patients with health care-associated infection (median, 9.0 days). Patients with MRSA tended to have longer hospital stays than patients with methicillin-sensitive strains (13 vs. 11 days). By clinical syndrome, median length of stay ranged from 8.0 days for persons with intravascular device-associated bacteremia to 15.0 days each for endocarditis and septic arthritis.

There were 21 fatalities for an overall case-fatality rate of 11%. The rate was 11% among both patients with health care-associated infections and among patients with underlying medical conditions. There were no fatalities in persons with no underlying medical conditions. Among persons with MRSA, the case-fatality rate was 14%. Both of these latter findings could have occurred by chance ( $P > .05$ ). Among persons with underlying medical conditions, mortality was associated with older age (0 of 39 persons <65 years old vs. 8 of 22 persons ≥65 years;  $P < .0001$ ). There was no association between mortality and age in the other 2 COSA groups.

## Discussion

To understand fully the epidemiology of community-onset MRSA, it is necessary to understand the epidemiology of all COSA infections. By using infections with bacteremia as an

easily definable “tip of the iceberg,” we found that COSA bacteremic infection with or without methicillin resistance is a serious health problem. Nearly half of all bacteremic infections with *S. aureus* occur in people living outside the hospital or long-term care setting. The incidence, 17 cases/100,000 persons, is nearly as high as that of invasive pneumococcal disease with bacteremia. In addition, at least in Connecticut, the incidence of community-onset MRSA infections with bacteremia is the same as that for invasive group A streptococcal disease with bacteremia. With a case-fatality rate of 11% and an average hospitalization of 11 days, a problem of this magnitude should rank high on the list of possible infectious disease public health concerns and should merit additional study. It is clear that the health impact of vancomycin-resistant *S. aureus*, once it is established, could be substantial both in and out of the hospital.

There are few data with which to compare the Connecticut incidence of COSA bacteremia. Although there has been growing interest in community-onset MRSA infections in recent years, we believe this study to be the first that attempts to define the population-based incidence of *S. aureus* bacteremia. Recent studies of COSA bacteremia have been hospital-based case series, in which population denominators were not used [4, 6, 16]. Although we learned much about risk factors for community-onset MRSA from these studies, including that its epidemiology is in part dependent on the amount of health care provided in the community setting [6, 12], it has been difficult to appreciate the full magnitude of the community problem. Given that COSA incidence rates were similar in the 3 surveillance areas without a tertiary-care hospital (New London, Stamford, and Waterbury) and that there was little difference between rural and suburban areas, the Connecticut experience suggests that COSA probably is a substantial problem elsewhere in the United States.

Our main descriptive epidemiological findings of COSA infections with bacteremia confirm observations in other published case series. Elderly persons and persons with underlying medical conditions are at particular risk for COSA, regardless of whether the organisms are methicillin sensitive or resistant [4–6]. In addition, we found consistently higher rates in more densely populated areas and among black persons in each of our study sites. These findings may reflect a higher prevalence in these groups with underlying medical and/or iatrogenic conditions that predispose to *S. aureus* infection. However, the possibility also exists that *S. aureus* colonization and, thus, disease rates could be higher in high-density populations. Studies comparing staphylococcal colonization rates in communities of high and lower population density could be of interest.

A major motivation for this study was to try to begin to understand how methicillin resistance fits into the community picture of *S. aureus* so that we can better understand what may happen if and when vancomycin-resistant *S. aureus* fully emerges. The source of *S. aureus* that causes community-onset infections, particularly when it is methicillin resistant, is of par-

ticular interest in this context. To try to differentiate MRSA that probably was generated in the hospital and acquired directly from health care system contact from MRSA that might have been acquired from contact with others in the community, we created 3 categories of COSA and MRSA infections. Of importance, we limited the definition of health care associated to persons who had been recently hospitalized or who had indwelling catheters, a group in which MRSA was highly likely to have come directly from recent health care system contact. Persons with underlying medical conditions who had not been recently hospitalized or who did not have indwelling catheters were not included in this group, although the majority may have had substantial outpatient health care contact. We created the intermediate group between health care intensive use and health care-naïve persons, because we think that understanding the extent to which MRSA now affects this group at high risk for invasive *S. aureus* infection is a critical first step to understanding the extent and population dynamics of MRSA spread. Others also have noted the need to distinguish between these factors [6, 10, 11].

Similar to the findings of recently published case series that examined either all COSA infections or were limited to MRSA infections or isolates [4–6, 16–18], we found that the majority ( $\geq 62\%$ ) of COSA bacteremias and the subset that were MRSA were health care associated and that most of the remaining persons had underlying medical conditions. In addition, the MRSA strains were multidrug resistant, which suggests that they were originally hospital generated. Of special note, the percentage of persons with MRSA was the same in the groups “hospital acquired” and “with underlying medical conditions.” This suggests either that health care system-generated methicillin-resistant strains are still largely confined to health care settings but are readily acquired in the outpatient medical setting among persons who are at high medical risk for serious *S. aureus* infections or that they are now widely circulating in the community setting.

It is clear that MRSA can circulate in the community and cause colonization and infection in people who have little interaction with the health care system [5, 7, 8, 19–24]. Nonetheless, it is important to understand better the dynamics of acquisition of multiply resistant MRSA among persons with underlying medical conditions. To the extent that their MRSA is directly acquired from interaction with the health care system, it may, in part, preventable through intensely applied infection control measures. It also would increase further the already substantial incentives to take aggressive efforts to try to contain vancomycin-resistant strains from the time they are first recognized [25, 26]. Unfortunately, because the group with no underlying medical conditions was small, our study could not conclusively determine the extent to which multidrug-resistant MRSA is circulating outside the outpatient health care setting in Connecticut.

Because our study has a number of important limitations, it

is only another step toward understanding the dynamics of COSA and community-onset MRSA. Further study to determine risk factors for MRSA in persons with underlying medical conditions is needed. Because we only looked at hospital records, we did not know the relative degree of interaction with the health care system of community-onset MRSA cases with underlying medical conditions, compared with that of their methicillin-sensitive counterparts. We also had no information on outpatient antibiotic use and did not use molecular epidemiological methods to compare nosocomial with community MRSA strains. Methods such as pulsed-field gel electrophoresis have been used in some studies to try to determine the extent to which MRSA in the community differs from MRSA that causes nosocomial infection [5, 7, 18, 27]. In addition, we only looked at bacteremic infections, not at localized infections without bacteremia, or at colonization. Both may be more sensitive for detecting MRSA that is genuinely circulating in the community. Nonetheless, it is conceivable that multidrug-resistant MRSA strains that originally arose in the hospital are now circulating widely outside it and that no substantive contact with the health care system is necessary to develop an infection with such strains. Given that MRSA that was not clearly health care associated was found in all 4 of our study sites, in areas with varying population density, and in persons with a variety of underlying medical conditions, it appears to be well established as a pathogen among persons at risk for serious *S. aureus* infections in Connecticut.

Continued population-based studies are needed. As efforts to prevent nosocomial and health care-associated *S. aureus* and MRSA infection continue, and given that the majority of COSA are currently health care associated, the potentially preventable fraction of *S. aureus* bloodstream infections is sizeable. Ongoing population-based monitoring can determine trends in the various levels of community-onset MRSA and *S. aureus* and should allow for a more accurate determination of the extent to which MRSA is the cause of serious infections in health care-naïve persons.

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