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Trends in Community Versus Health Care-Acquired Methicillin-Resistant *Staphylococcus aureus* Infections

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Abstract Since the first clinical isolate of methicillin-resistant *Staphylococcus aureus* was described in 1961, this pathogen has established itself as a leading cause of health care-associated infections. More recently, MRSA has become a relatively common cause of infection among persons without typical health care-associated risk factors and is now the most common cause of community-onset purulent skin and soft-tissue infections in many regions of the USA. The appearance of "community-associated" MRSA is not due to the expansion of health care-associated MRSA into the community but rather the result of the independent emergence of a novel clone of MRSA. There are some encouraging data to suggest that the incidence of MRSA infection, particularly invasive infections, is decreasing in the USA, but this pathogen remains a common cause of infection associated with substantial morbidity and mortality. Thus, there is ongoing need for effective and safe prevention, diagnosis, and treatment strategies.

Keywords *Staphylococcus aureus* · Methicillin resistance · Antimicrobial resistance · Infection · Epidemiology

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Introduction

Methicillin-Resistant *S. aureus* in Health Care Settings and the Community: A Tale of Two Merging Epidemics

Methicillin-resistant isolates of *S. aureus* were first reported in 1961 [1]. This occurred shortly after methicillin, the first of several semisynthetic penicillinase-resistant penicillins, had been developed and introduced into clinical practice in response to the emergence and spread of penicillin-resistant *S. aureus* that had made penicillin ineffective for the treatment of most *S. aureus* infections by the 1950s. Over the following decades, methicillin-resistant *S. aureus* (MRSA) became an increasingly common cause of health care-associated infections (HAIs), occurring almost exclusively among persons with identifiable health care-associated risk factors such as hospitalization, presence of invasive medical devices (e.g., central venous catheters), surgery, and dialysis. By the 1980s and 1990s, MRSA had become endemic in most hospitals in the USA and in many other regions of the world. In many hospitals, methicillin-resistant strains of *S. aureus* had become more common causes of HAIs than methicillin-susceptible strains. By 2004, MRSA accounted for 63% of *S. aureus* isolates from HAIs in intensive care unit patients in the USA. In a recent report from the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN), *S. aureus* was the second common most pathogen identified in device-associated (i.e., central line-associated bloodstream infections (CLABSI), catheter-associated urinary tract infections, and ventilator-associated pneumonia) and procedure-associated (i.e., surgical site infections) infections reported between 2011 and 2014 [2]. Rates of methicillin resistance among these isolates ranged from 42 to 57%, varying by infection site and year.

Beginning in the late 1990s, reports of MRSA infections among persons without typical health care-associated risk factors began to emerge. These "community-associated" MRSA infections, most commonly skin and soft-tissue infections (SSTI), were first described among children in the Midwest region of the USA [3, 4]. Study of phenotypic (e.g., antimicrobial resistance profiles) and genetic characteristics of isolates from these community-associated MRSA infections revealed that these cases were not simply due to spread of health care-associated MRSA clones within the community but rather to the emergence of a novel clone of MRSA, now known as pulsed-field type USA300. This clone was notably different from common health care-associated clones (e.g., pulsed-field type USA100), including susceptibility to a number of non-beta-lactam antibiotics to which health care-associated strains were typically resistant (e.g., clindamycin, levofloxacin) and the production of several enzymes and toxins that was not common on health care-associated strains (e.g., the Panton-Valentine leucocidin). The initial reports were closely followed by recognition of rapid clonal spread of this community-associated MRSA clone across the USA. By 2004, MRSA had become the most common cause of purulent skin and soft-tissue infections presenting to emergency departments around the USA [5]. It is worth noting that MRSA did not just replace methicillin-susceptible *S. aureus* infections but rather there was a dramatic increase in the absolute number of SSTI, particularly purulent SSTI associated with the emergence of this new community-associated MRSA clone [6, 7], suggesting that it was better able to cause disease than some other strains of MRSA.

Although the epidemiology of health care-associated and community-associated MRSA strains was initially quite distinct, the boundaries of these two epidemics have begun to overlap substantially in recent years as USA300 spread and caused disease within communities and in health care facilities. Data from individual hospitals [8, 9] and from national surveillance systems [10] show that community-associated MRSA clones now cause a substantial proportion, and may even be responsible for the majority, of MRSA HAIs in many health care facilities. In a study of *S. aureus* isolates collected from patients at 43 US academic medical centers in 2011, USA300 was the most common MRSA PFGE type identified, representing 61% of MRSA isolates, and was responsible for 37% of nosocomial infections [11]. Similarly, CDC data from 2015 suggest that MRSA strains of the USA300 PFGE type were responsible for nearly as many cases of health care-associated invasive MRSA disease as USA100 strains (33.3 versus 37.9%, respectively) [10].

Definitions of "Health Care-Associated" and "Community-Associated" Applicable to MRSA

There are currently several different strategies used to classify MRSA infections or MRSA isolates as health care associated or community associated. Classification is typically based upon either epidemiologic factors related to the patient or the infection (e.g., location at the time of onset of infection, identified risk factors for MRSA acquisition) or characteristics of the MRSA isolate (e.g., genetic characteristics, antimicrobial susceptibility profile). Decisions regarding which classification schema to use are typically based upon the purpose of classification and available resources. For HAI surveillance purposes, clinical definitions based on health care exposures and the timing of the onset of infection, rather than genetic characteristics of the organism, may be most useful given that clones that fulfill genetic or resistance phenotype definitions of "community-associated" MRSA are becoming increasingly common causes of infections that occur as a result of the receipt of health care. On the other hand, when the purpose of classification is for the study of the epidemiology of specific MRSA clones, genetic characteristics would be more appropriate than clinical or phenotypic characteristics for the same reason and because some isolates of community-associated MRSA clones exhibit resistance patterns that are similar to classic health care-associated clones.

Definitions Based on Risk Factors for MRSA or the Timing of Specimen Collection

The CDC's NHSN provides surveillance definitions for identification of health care-associated infections that can be applied to MRSA surveillance. Laboratory-identified (LabID) Event surveillance definitions use only laboratory testing data and dates of hospital admission and discharge to classify MRSA as well as other multidrug-resistant organisms and *C. difficile* [12]. In these definitions, a health care facility-onset MRSA event is one in which the specimen from which MRSA was identified was collected more than 3 days after the patient's admission to the facility. Community-onset events, on the other hand, are those in which the specimen was collected in an outpatient location or an inpatient location within the first 3 days after admission to the facility.

Unlike LabID Event surveillance definitions, the NHSN clinical surveillance definitions incorporate clinical information, such as signs and symptoms, physical exam findings, and the results of imaging studies and other tests, to classify infections [13]. Using these definitions, an infection would be classified as a health care-associated infection if the date of the infection, based on NHSN site-specific infection criteria, occurs on or after the third calendar day of admission to an inpatient location. Infections are considered to be present on admission if the date of the infection is prior to admission or on the day of admission or the first calendar day after admission.

For MRSA surveillance and research purposes, however, it may also be useful to include an assessment of recent health care exposures. For example, the CDC's Active Bacterial

Core surveillance (ABCs) system uses an assessment of health care risk factors to classify cases in which MRSA was isolated within the first 3 days of hospitalization as either "community-associated" or "health care-associated community onset" [14•]. Using this method, health care-associated community-onset cases are those where the culture was obtained as an outpatient or before the third hospital day from a person with documented health care risk factors (i.e., presence of an central venous catheter at time infection, or a history of MRSA colonization or infection, surgery, hospitalization, dialysis, or residence in a long-term care facility in the 12 months preceding the culture).

Definitions Based on Characteristics of the Organism

Because community-associated MRSA strains are often found to be susceptible to several antimicrobial agents and classes (e.g., clindamycin, fluoroquinolones) to which health care-associated strains are usually not susceptible, some have used phenotypic antimicrobial susceptibility profiles to classify MRSA isolates as either health care associated or community associated. However, in recent years, an increasing proportion of community-associated strains are found to be resistant to these agents [15, 16]. Thus, as differences in antimicrobial susceptible profiles of community- and health care-associated MRSA strains become less pronounced, the use of antimicrobial resistance phenotypic characteristics to classify individual isolates may increasingly lead to misclassification.

A number of genetic and molecular characteristics have been found to serve as useful differentiators between community-associated and health care-associated MRSA clones. The mechanism of resistance to the antistaphylococcal penicillins, such as methicillin, is production of an altered penicillin-binding protein, PBP 2a, with low affinity for binding beta-lactam antibiotics. PBP2a is encoded by the *mec*A gene, which is located on a staphylococcal cassette chromosome (SCC). SCC*mec* typing is one strategy that is commonly used to classify isolates. For example, health care-associated MRSA clones most commonly possess SCC*mec* types I–III, whereas the epidemic USA300 clone of community-associated MRSA possesses SCC*mec* type IV. Pulsed-field gel electrophoresis (PFGE) is also commonly used to classify or categorize MRSA isolates. For example, PFGE type USA100 (the "New York/Japan" clone) is the most common health care-associated MRSA PFGE type in the US. USA200 (EMRSA-16 clone) and USA500 (also known as the Iberian clone) are other relatively common health care-associated MRSA clones, whereas USA300 as well USA400, USA1000, and USA1100 PFGE types are among the most common community-associated MRSA clones. Other genetic characteristics that have been used to classify MRSA isolates as community or health care associated include multi-locus sequence type, presence or absence of specific toxins, enzymes, and genes (e.g., the Panton-Valentine leucocidin (PVL) and arginine catabolic mobile element (ACME) are commonly found in USA300 community-associated MRSA strains) [17, 18•].

Secular Trends in MRSA Infection

Several data sources suggest that the overall incidence of MRSA infection is decreasing in the USA. For example, the CDC's ABCs system receives detailed information about cases of invasive MRSA infection, defined as isolation of MRSA from a normally sterile body site, from nine metropolitan areas within the USA. These data provide estimates of the burden and characteristics of invasive MRSA infection in the USA. Between 2005 and 2011, the overall incidence of invasive MRSA infection was found to have decreased by 31.2% (from 37.5 to 25.8 per 100,000 persons), representing an estimated 30,800 fewer invasive MRSA infections in 2011 [14•]. This reduction included a 54.2% reduction in hospital-onset disease and a 27.7% reduction in health care-associated community-onset disease. Community-associated infections were found to have decreased by 5% (5.6 to 5.3 per 100,000 persons). By 2015, the overall rate of invasive MRSA infection had further decreased to 18.8 per 100,000 persons [10]. Despite the observed increase in MRSA infections among persons without health care-associated risk factors, the ABCs data suggest that exposure to health care remains a major risk for development of invasive MRSA infections. In 2015, 78% of cases were classified as health care-associated (incidence 14.8 per 100,000) while 21% were classified as community-associated (incidence 3.9 per 100,000) [10]. The majority (79%) of the health care-associated infections had their onset in the community rather than in the hospital. During this most recent time period, approximately 84% of identified cases involved MRSA bloodstream infections with (67%) or without (33%) another identified focus of infection. Localized infectious syndromes commonly identified among cases of invasive MRSA infection included SSTI (22% of cases), osteomyelitis (15%), pneumonia (13%), and endocarditis (6%).

Similarly, data from CDC's health care-associated infection surveillance systems have shown substantial reductions in hospital-onset CLABSI caused by MRSA between 1997 and 2007 [19]. Over this 11-year period, the incidence of MRSA CLABSI was observed to increase from 1997 to 2001 and then decline from 2001 to 2007, with a significant overall estimated decline of 49.6%. Of note, similar decreases were seen in rates of methicillin-susceptible *S. aureus* (MSSA) CLABSI and overall rates of CLABSI suggesting that the reductions in MRSA infections may not reflect MRSA-specific epidemiological changes or interventions but rather broader changes in the epidemiology of CLABSI, such as

implementation of horizontal infection prevention strategies (e.g., the "central line bundle"). In recent years, hospitals participating in the Centers for Medicare and Medicaid Services Inpatient Prospective Payment System have been required to submit data for all cases of MRSA bacteremia to the CDC's NHSN. Such infections may represent CLABSI or MRSA bloodstream infections that arise from another focus of infection (e.g., MRSA surgical site infection with secondary MRSA bloodstream infection), and thus, may provide a broader view of invasive MRSA disease among hospitalized patients. Data reported by 3949 US hospitals between 2011 and 2014 demonstrate a 13% decrease in hospital-onset MRSA bacteremia, defined as isolation of MRSA from a blood culture obtained after the third day of hospitalization, with a statistically significant 4% decrease observed between 2013 and 2014 [20].

In addition to causing invasive infections, MRSA is also a common cause of skin and soft-tissue infections that, unless accompanied by bloodstream infection or infection at another normally sterile body site, are not included in studies of invasive MRSA infections. Thus, the overall burden of MRSA disease may be substantially underestimated in the previously described studies. In fact, contrary to reported downward trends in invasive MRSA infections and hospital-onset CLABSIs beginning between 2001 and 2005 [10, 14•, 19], data from the University HealthSystem Consortium showed that rates of MRSA-associated hospitalizations at US academic medical centers increased from 20.9 to 41.7 per 1000 hospitalizations between 2003 and 2008 [21]. Investigators using different data sources to estimate the burden of MRSA hospitalizations in the USA similarly reported a doubling of the number of MRSA-associated hospitalizations between 1999 and 2005 [22] with a subsequent slowing and stabilization of MRSA hospitalization rates between 2005 and 2009 [23]. In that study, there were an estimated 463,017 MRSA-related hospitalizations (11.74 per 1000 hospitalizations) in 2009, demonstrating that, despite evidence of some progress, MRSA infections remain a significant public health concern.

While these overall trends are important to recognize, they may not reflect the epidemiology of MRSA infection within specific patient populations or the epidemiology of specific MRSA clones (e.g., USA300). The pediatric population is one such population in which trends differ from those of the general population. In the previously described study of MRSA CLABSI, for example, significant decreases were observed in all types of intensive care units with the notable exception of pediatric units where rates remained unchanged over time [19]. When the CDC's ABCs data on invasive MRSA infections are restricted to the pediatric population, unlike the findings in the overall population, there were no significant changes in the incidence of hospital-onset or health care-associated community-onset disease between 2005 and 2010 and there was a 10.2% yearly increase in the incidence of community-associated MRSA infections during that period [24]. In this population, community-associated infections were the single most common type of invasive MRSA infection, accounting for 42% of cases, while hospital-onset disease and health care-associated community-onset disease accounted for 35 and 23% of cases, respectively. In all three categories of infection, USA300 isolates accounted for the largest proportion of cases, ranging from 54.5% of hospital-onset cases to 84.3% of community-associated cases. Differences existed within subpopulations of pediatric patients as well. For instance, the incidence of infection was higher in infants less than 90 days of age, in whom 80% of infections were hospital onset, than in older infants and children and higher among black children compared to others.

There are, however, some encouraging data from the pediatric population, particularly in studies that have included data from more recent years. In a study that used electronic medical record data from 348 neonatal intensive care units across the USA, the incidence of invasive MRSA infection increased from 1997 to 2006, peaking at approximately 20 per 10,000 infants [25]. After 2006, the incidence of MRSA infection moderately decreased through 2012 but remained above that observed during the earliest years of the study period. Of note, the incidence of MSSA infection followed similar trends and was higher than that of MRSA throughout the study period. In an evaluation of all 41,745 *S. aureus* isolates recovered from pediatric patients receiving care through the US Military Health System between 2005 and 2014, the proportion of isolates resistant to methicillin was observed to increase from 40.6% in 2005 to 46.4% in 2007 and then steadily decrease to 31.6% by 2014 [26]. Perhaps not surprisingly, nearly 78% of isolates were from SSTI. These SSTI isolates had the highest rates of resistance, peaking at 50.8% in 2007 and reaching a nadir of 34.5% in 2014, a statistically significant change. Of note, the total number of *S. aureus* isolates per year also decreased over the evaluated period, suggesting a decrease in the overall burden of *S. aureus* infections within this population.

Persons requiring chronic hemodialysis have long been recognized as a population with a rate of MRSA infection substantially greater than that observed in the general population. ABCs data demonstrate that invasive MRSA infections among chronic hemodialysis patients have decreased from 6.5 to 4.2 per 100 dialysis patients (a 7.3% decrease per year) between 2005 and 2011 [27]. Despite this improvement, the rate of MRSA infection in this population remains markedly elevated as compared to the general population. Bloodstream infections among outpatient hemodialysis patients as reported to the CDC's NHSN system by 6005 outpatient hemodialysis facilities in 2014 demonstrate that *S. aureus* remains the most common cause of bloodstream infection in this population, accounting for 30.6% of the 29,516 reported bloodstream infections, and that MRSA is responsible for a large proportion (40%) of these *S. aureus* bloodstream infections [28].

Another population worthy of mention is that of the Veterans Affairs (VA) medical facilities. Between 2007 and 2015, monthly MRSA HAI rates in these facilities decreased by 87% in intensive care units, 81% in spinal cord injury units, 80% in non-intensive care units, and 49% in long-term care facilities [29]. These reductions were temporally associated with the introduction of the VA MRSA Prevention Initiative which included universal nasal surveillance for MRSA carriage, contact precautions for patients colonized or infected with MRSA, hand hygiene, and institutional culture change related to infection prevention and control practice and individual responsibility [30].

Evolving Antimicrobial Resistance Among MRSA Isolates

Community-Associated MRSA Strains

Initially, community-associated MRSA strains (e.g., USA300) demonstrated higher rates of susceptibility to several non-beta-lactam antibiotics, such as clindamycin and fluoroquinolones, than typical health care-associated strains. In more recent years, however, isolates resistant to these agents have been reported with increasing frequency. In a study of over 8000 MRSA isolates collected from 143 US medical centers between 2012 and 2014, 34% of community-associated isolates demonstrated either constitutive or inducible resistance to clindamycin (as compared to 55% of health care-associated isolates) and 64% of community-associated isolates were resistant to levofloxacin (as compared to 79% of health care-associated isolates) [15]. Trimethoprim-sulfamethoxazole and tetracycline, on the other hand, were found to have activity against ≥ 97.7 and ≥ 95.3% of community-associated and health care-associated MRSA isolates, respectively. Other agents known for their activity against MRSA (e.g., vancomycin, daptomycin, and linezolid) demonstrated activity against ≥ 99.9% of community- and health care-associated isolates. In that study, community-associated MRSA was defined as an MRSA isolate obtained from an outpatient or from a hospital inpatient within the first 48 h of admission. In a study of MRSA isolates from eight hospitals in the greater New York metropolitan area that used PFGE typing to classify isolates, 78 (64%) of 121 isolates from 2013 to 2014 were USA300 strains and 25 (21%) were USA100 strains [16]. Seventy-one percent of isolates (including 69% of USA300 and 80% of USA100 isolates) were resistant to at least three different classes of antibiotics. USA300 isolates were frequently resistant to non-beta-lactam antibiotics, including fluoroquinolones (72% of isolates were resistant) and clindamycin (17% of isolates were resistant). This increasing rate of resistance among community-associated MRSA isolates to agents such as clindamycin and fluoroquinolones is reflected in the current clinical guidelines which do not recommend the use of these agents for empiric treatment of purulent skin and soft-tissue infections [31••].

Vancomycin-Resistant MRSA

Vancomycin has long served as a first-line agent for the treatment of MRSA infections. The first case of vancomycin-resistant MRSA in the USA was reported in 2002 but, fortunately, vancomycin resistance among MRSA isolates has remained quite rare. As of February 2015, a total of 14 isolates of vancomycin-resistant MRSA have been reported in the USA [32]. Each of these cases appears to be an independent event due to acquisition of the *vanA* operon by MRSA due to transfer from vancomycin-resistant *Enterococcus* (VRE) in patients co-colonized with both MRSA and VRE. Of the 14 identified cases, 13 have involved health care-associated strains of MRSA. The thirteenth case occurred in a patient with known colonization with MRSA of community-associated lineage [33]. Thus far, there has been no evidence of transmission of vancomycin-resistant MRSA to persons with close contact with the index cases.

Outcomes Associated with MRSA Infection

Invasive MRSA infection has long been associated with a high rate of mortality. In a recent report, CDC designated MRSA as a "serious" antibiotic resistance threat, based on estimates of 80,461 invasive MRSA infections resulting in 11,285 deaths per year in the USA [34]. In 2011, data from the CDC's ABCs system showed that among the 4872 cases of invasive MRSA infection, the all-cause mortality rate was 13% [14•]. Death was more common among hospital-onset cases (21%) than health care-associated community-onset or community-associated cases (12 and 10%, respectively, $p < 0.001$). It is unknown, however, if the observed differences in mortality seen among these three groups are related to differences in the organisms causing infection, the site of infection, patient-specific factors, or other factors. Based on these data, the investigators estimated an overall all-cause mortality rate associated with invasive MRSA infections in the USA of 3.62 per 100,000 persons, ranging from 0.57 for community-associated disease to 1.95 for health care-associated community-onset disease. These estimates represent a 31% decrease in the overall mortality rate of 7.13 per 100,000 persons that was observed in 2005. The greatest decrease in mortality was observed among hospital-onset cases (54.2% decrease), followed by health care-associated community-onset (27.7% decrease), and community-associated cases (5.0% decrease).

Conclusions

Over the past 20 years, there have been major changes in the epidemiology of MRSA infection as novel clones of MRSA emerged and rapidly spread among persons without typical health care-associated risk factors. The emergence of

community-associated MRSA was associated with an increase in the incidence of purulent skin and soft-tissue infections and establishment of MRSA as the most common cause of this type of infection in many regions of the USA. The past decade has seen substantial decreases in the incidence of health care-associated MRSA infections and there are encouraging data that suggest that the incidence of community-associated MRSA infections may also be diminishing. MRSA infection, however, remains a substantial cause of morbidity and mortality among persons with and without health care-associated risk factors.

Compliance with Ethical Standards

Conflict of Interest No potential conflicts of interest relevant to this article were reported.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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