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Staphylococcus aureus: Changing Epidemiology and Mechanisms of Resistance

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Introduction

Antimicrobial resistance among *Staphylococcus aureus* (*S. aureus*) isolates is a problem in the community setting throughout the United States. This article describes characteristic features of the epidemic of methicillin-resistant *Staphylococcus aureus* (MRSA) that is occurring in communities throughout the United States. Questions that are addressed include: What is the prevalence of community MRSA infections across the country? How has community MRSA evolved over the past decade in the United States? How are the MRSA strains similar or different across communities? Are there genetic differences observed in community versus hospital strains or among communities? How are MRSA mechanisms of resistance evolving? How are these infections being transmitted?

Case Study: A 39-year old software engineer working with a start-up company was recently admitted to my medical service. He had no health insurance. He is a smoker and he drinks alcohol socially. His last visit to a physician was when he was

Figure 1

Chest X-ray of a man with lung abscess due to community-onset MRSA. Note the air fluid level.

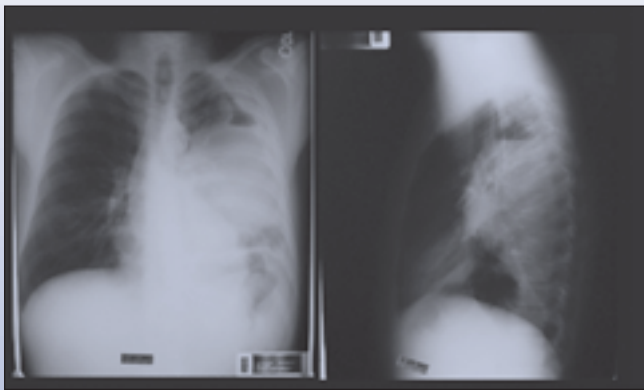
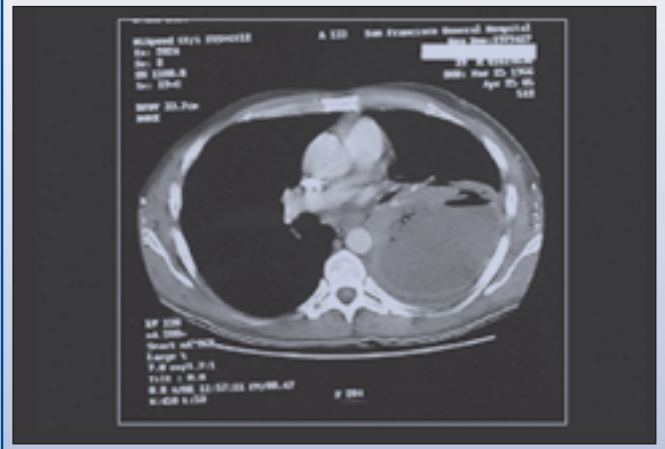


Figure 2

CT Scan of the chest for the patient with lung abscess



inducted into the military 20 years previously. He has no history of medications, chronic illnesses, or hospitalizations. He reports a four month illness with chest pain and shortness of breath, followed by a period of recovery and then a second illness with one to two months of fever, chills, sweating, shortness of breath, productive cough and a 15-lb weight loss. In his initial chest x-ray, there is a dense infiltrate in the left lung field. An air fluid level at the top is visible laterally and anteriorly (**Figure 1**). The possibility of an anaerobic lung infection was considered but an extensive dental examination determined that his teeth and gums were healthy. An abscess was visible on the CT scan (**Figure 2**). A culture of the abscess fluid, obtained at the time of chest tube placement, revealed MRSA with a community drug-resistance phenotype.

This case study represents a significant change occurring in the demographics of MRSA infections. As in this case, patients without risk factors classically associated with infections caused by antibiotic-resistant strains are increasingly encountered in the

community. Because there is no national surveillance program for community staphylococcal infections in the United States, physicians must rely upon reports of these infections in the published medical literature. A recent PubMed search using the key terms “community” and “methicillin-resistant *Staphylococcus aureus*” indicated an exponential increase in articles pertaining to community-associated MRSA over the past several years. These resistant strains have now been described throughout the continental United States, Alaska, and Hawaii – a remarkable change over a five to ten year period.

Evolution of a community-associated MRSA epidemic

The pattern of the rate of occurrence of community-associated MRSA is likely to be comparable to the epidemic that occurred with penicillin-resistant *S. aureus* strains after the introduction of penicillin in the 1940's. Approximately two decades following penicillin's introduction, there was a significantly increased prevalence of penicillinase-producing *S. aureus* isolated from community-onset infections. Presently, hospital and community rates of penicillin-resistant *S. aureus* strains are indistinguishable.

One of the early indications that MRSA strains were invading the community was that patient populations not typically associated with MRSA infections (e.g., children, prison inmates, sports teams) were acquiring infections caused by these MRSA strains. Community MRSA outbreaks have subsequently been reported in numerous populations including military recruits, native populations, homosexual males, HIV+ patients, football teams, wrestlers, gymnasts, fencing teams, injection drug users, and homeless populations.¹⁻⁷

Community versus hospital MRSA: genetic differences

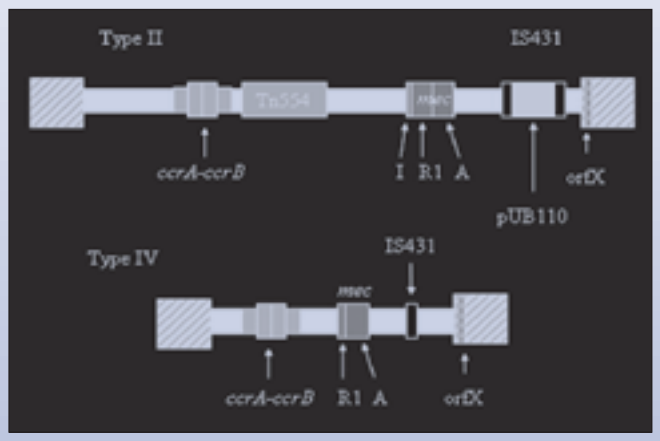
Community strains often are associated with outbreaks, generally in populations lacking risk factors for MRSA, and these strains are members of specific clones that are genotypically different from those found in the hospital setting. While nosocomial strains are often resistant to multiple drugs, community strains tend to be susceptible to many antibiotics. The genetic element, staphylococcal chromosomal cassette (SCCmec),⁸ that carries the gene (*mecA*) mediating methicillin resistance in staphylococci is a novel one in community MRSA strains. Prior to the identification of the community-associated strains, there were three types of SCCmec elements that had been recognized in nosocomial strains. The very first community MRSA isolate to be genotypically characterized, the MW2 strain, was found to have a fourth type. This type IV element is now known to be a hallmark feature of community MRSA.⁸⁻¹⁰ A

type V element has more recently been identified and others are likely to follow.

SCCmec types vary in size and genetic content. The size of the four most common SCCmec elements varies from approximately 20,000 base pairs up to 60,000 base pairs. This element contains two recombinase genes (*ccrA* and *ccrB*) that

Figure 3

The two most common types of the SCCmec element cassettes found in MRSA isolates in the United States, Type II and Type IV. Tn554 is a transposon encoding macrolide resistance. IS431 indicates insertion sequences and pUB110 is an integrated plasmid encoding tobramycin resistance. The methicillin resistance gene cluster includes the structural gene, *mecA*, which encodes the low affinity penicillin binding protein 2A; and two regulatory elements, *mecI* and *mecR1* which encode a repressor protein and a signal transducing protein respectively, which because of a deletion mutation are nonfunctional in the Type IV element. *ccrA-ccrB* are genes for the recombinations that excise and insert SCCmec into the open reading frame of *orfX* of the *S.aureus* chromosome.



recognize a specific site with a gene of unknown function, *orfX*, on the host genome into which SCCmec can be integrated or excised. It can be thought of as a genomic parasite because the element requires the host genome for its propagation. It cannot replicate on its own, and once integrated into the genome, it depends on the host genome for its own success.

The two most common types of the SCCmec elements found in US clinical isolates are type II and type IV (Figure 3). The absence of resistance genes, other than *mecA*, on type IV SCCmec of community MRSA strains is one reason that these strains are more susceptible to multiple drugs than the hospital strains, which often carry the type II element.⁹ The type II element in addition to *mecA* carries a transposon (Tn554), which codes for resistance to erythromycin and spectinomycin, and an integrated plasmid (pUB110) that confers resistance to tobramycin, kanamycin, and bleomycin (Figure 4).¹¹ Hospital strains therefore tend to be more resistant because the type II element is a multiple drug resistance determinant.

Another distinguishing feature of the type IV element is its relatively small size. The size of the type IV element is within a range that allows it to be mobilized by a bacteriophage and transferred to another strain via transduction.^{8,9} Types I, II, and III are above the range allowing them to be easily packaged and transferred by phage. With the evolution of the smaller type IV element, SCCmec is better able to move into different genetic backgrounds. Similar to the plasmid epidemic that occurred with penicillinase production 20 years ago, we now have a chromosomal element that appears to be small enough to parasitize numerous host strains.

Panton-Valentine Leukocidin (PVL) cytotoxin linked with severity of community-associated MRSA

Emergence and virulence of community-associated MRSA have been linked to the cytotoxin, Panton-Valentine leukocidin (PVL), which was described in the 1930s.^{9,10,13} This is a two-component cytotoxin that lyses polymorphonuclear neutrophils. Because

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of this biological activity PVL has been postulated to increase the severity of the disease and perhaps to contribute to the epidemic of these MRSA clones. PVL is rare in hospital isolates and in methicillin-susceptible strains.

In the United States, there are two predominant clones that are associated with community MRSA strains, both of which contain PVL: USA300 (a sequence type 8 strain), which is the predominant strain in San Francisco and the southeastern United States; and USA400 (MW2, a sequence type 1 strain), which was the original community MRSA clone to be identified and a predominant one in Alaska and in the Mid West. These two strains together account for approximately 80% of the MRSA community strains. Both of these strains contain the SCCmec element and both have been implicated in severe disease. These virulent strains are recognized for their ability to cause severe furunculosis in skin and soft tissue infections, which often tend to recur. Necrotizing pneumonia (post-influenza in children) has been associated with strains that carry PVL.¹⁴ PVL-positive MRSA strains have been associated with necrotizing fasciitis,¹⁵ an extremely uncommon staphylococcal infection.

Origins of community-associated MRSA

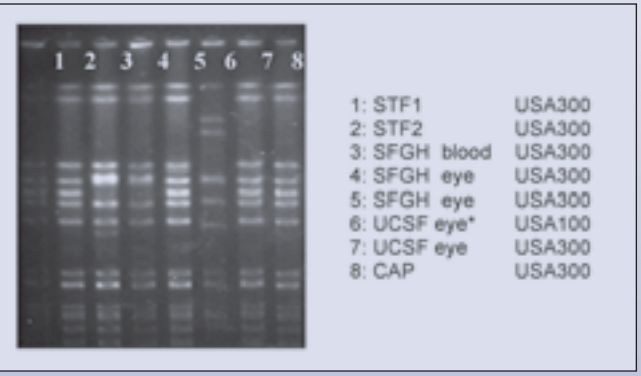
Community-associated MRSA clones may have originated from three potential sources.¹⁶ Strains of the USA300 clone type appear to be feral descendants of the same highly successful nosocomial lineage as COL, the very first clinical isolate of MRSA, and other related nosocomial MRSA strains. Community MRSA may also be descended from an endemic community isolate: sequence type 1 MRSA strains, similar to MW2, were identified in aboriginal populations of Australia years ago, although these strains do not carry PVL genes.^{17,18} Finally, evidence suggests that some community methicillin-susceptible strains may acquire SCCmec and be recruited into the cadre of methicillin-resistant strains while retaining the fitness, virulence, and epidemic features associated with community *S. aureus* strains.

Transmission of community-associated MRSA and prevalence of USA300 strain

Approximately a third of normal individuals carry *S. aureus* in the anterior nares. The organism is transmitted by direct contact, probably through the hands in most instances. Contact sports,

Figure 5

Pulsed field gel electrophoresis patterns of some MRSA isolates from San Francisco Bay Area patients for the period of 2004-2005. STF1 and STF2 (lanes 1 and 2) are USA300 clone type strains from epidemiologically related cases of endocarditis seen in a San Francisco private hospital. SFGH blood (lane 3) is a bloodstream isolate of USA300 from a patient with bacteremia admitted to San Francisco General Hospital (SFGH). Lanes 4, 5, and 7 are USA300 isolates from unrelated cases of periorbital infections seen at SFGH and at the University of California Medical Center (UCSF). Lane 8 is an isolate of USA300 from a case of community-associated MRSA pneumonia in a fourth Bay Area hospital. Lane 6 is a nosocomial eye infection caused by a MRSA strain of the USA100 lineage.



such as football and wrestling, have been implicated in community MRSA outbreaks. One such outbreak involved two professional football teams.¹⁹ Abrasions occurring on turf probably led to inoculation and/or colonization of individuals and subsequent transmission within the locker room. All of the *S. aureus* isolates were of the USA300 clonal lineage. This same clone has been involved in numerous outbreaks of members of sports teams, military recruits, and prison and jail inmates.

In San Francisco, MRSA isolates, and the USA300 clone in particular, are quite pervasive. The overall number of MRSA clinical isolates each year is on the order of one for every 100-200 individuals on average, and the USA300 clone is present in every hospital. The spectrum of illness is quite broad. For example, the isolates designated STF1 and STF2 in **Figure 5** were USA300-type strains from a husband and wife, both injecting drug users, who presented within one week of each other with endocarditis. USA300 has been responsible for several cases of periorbital infections (isolates 3-5 and 7 in **Figure 5**) and, as others have reported elsewhere, with community associated pneumonia (isolate 8 in **Figure 5**).

The USA300 strain is the predominant one at San Francisco General Hospital and is prevalent in both outpatient and inpatient populations. Approximately 85% of all MRSA isolates are the USA300 clone. The clone is prevalent in several Bay Area hospitals, accounting for about 70% of MRSA isolates overall. A significant paradigm shift is that the majority of MRSA isolates are no longer from patients with nosocomial infections, but from patients with community-onset infections.

In summary, current patterns of infections and outbreaks caused by community-associated MRSA, particularly those belonging to the USA300 clone, indicate that MRSA strains are becoming the norm throughout the United States. Community strains of MRSA are fit and able to cause serious, invasive disease. MRSA can no longer be considered as an exclusively hospital pathogen and clinicians should expect to encounter these strains in their everyday practices.

Figure 4

Characteristics of SCCmec element cassettes. The genes that are present in the four most common SCCmec types vary among these elements. The regulatory genes, mecR1-I are deleted (Δ) in type I and IV. The tobramycin-resistance encoding plasmid pUB110 is present on in type II. The type III element has an integrated tetracycline-resistance plasmid, pT181. In addition to methicillin resistance, the type II and type III elements also carry other resistance genes, including erythromycin (erm), tobramycin (tobra), tetracycline (tet), or mercury (Hg).

SCCmec				
	I	II	III	IV
Size	34 kb	53 kb	67 kb	21-24 kb
mecR1-I	Δ	+	+	Δ
pUB110	-	+	-	-
pT181	-	-	+	-
IS431	1	2	4	1
Resistances	None	Erm, tobra	Erm, Tet, Hg	None

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Target Audience: Practicing physicians, infectious disease physicians, hospital epidemiologists, clinical microbiologists, pharmacists, public health authorities, and others interest in the treatment of *S. aureus* bacteremia and endocarditis.

Learning Objective: After reading this publication, the reader should be able to recognize the changing epidemiology and mechanisms of resistance among *Staphylococcus aureus* isolates.

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(At least three of the four answers must be correct in order to obtain a CME certificate)

See mailing instructions and other pertinent information on the reverse side.

- 1) Community-associated MRSA (CA-MRSA) infections have been described in all of the following groups except:
- a) Inmates in correctional facilities
 - b) Hospital nurses
 - c) Military recruits
 - d) Football players
 - e) Injection drug users

Answer: _____

- 2) USA300 and USA400 strains account for approximately 80% of all the CA-MRSA in the United States
- a) True
 - b) False

Answer: _____

- 3) CA-MRSA isolates:
- a) Contain a small, mobile genetic component, the type IV SCCmec element
 - b) Are often contaminants when grown from a single blood culture
 - c) Display antimicrobial resistance patterns similar to those of hospital-associated MRSA
 - d) Usually lack Panton Valentine leukocidin (PVL)
 - e) Do not colonize the anterior nares of normal adults

Answer: _____

- 4) Clinical infections associated with CA-MRSA infection include all except:
- a) Necrotizing pneumonia
 - b) Recurrent folliculitis
 - c) Deep skin and soft tissue infection
 - d) Recurrent urinary tract infections

Answer: _____

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