

Methicillin-Resistant *Staphylococcus aureus* (MRSA): Prevalence and Epidemiology Issues

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Awareness of the threat of MRSA is growing. Scientists have put a lot of effort into trying to divide and classify MRSA strains into groups to better understand it. This led to the discovery that the resistance gene, *mecA*, and surrounding DNA could be grouped into several types. It was also discovered that the MRSA strains that caused hospital-acquired (nosocomial) infections were different strains than those seen in the communities. Several studies led to the realization that the number of MRSA infections is increasing, that more *Staphylococcus aureus* infections are caused by MRSA strains, and that the community strains are now showing up in the hospital. There have been government initiatives to try to decrease MRSA infections, with the most perplexing issue being that of whether or not to perform surveillance cultures on as many people as possible to eradicate MRSA from the community, as well as the hospital.

INDEX TERMS: MRSA, methicillin-resistance, *Staphylococcus aureus*, prevalence, epidemiology

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LEARNING OBJECTIVES

1. Differentiate between community-acquired and hospital-acquired MRSA.
2. Describe the various MRSA typing systems.
3. Discuss the change in number of MRSA infections and percentage of MRSA isolates in the U.S.

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4. Describe what is included in the APIC guidelines and the SHEA report in regards to the elimination of MRSA.

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Wanda Reygaert PhD is the Focus: Methicillin-Resistant Staphylococcus aureus guest editor.

Until a few years ago, the risk associated with MRSA infections was primarily considered a nosocomial issue. But then a growing number of infections were noted as originating in the non-hospital population and studies were initiated to characterize the differences between hospital-acquired (nosocomial) MRSA (HA-MRSA) and community-acquired MRSA (CA-MRSA). Certain criteria were identified to try to distinguish between these. The now accepted designation for CA-MRSA is those strains of MRSA that are isolated from infections in out-patient settings or from hospitalized patients within 48 hours of hospital admission. In addition, these patients must not have had a previous MRSA infection, and must not have been a patient in a hospital or nursing home, or have had dialysis or surgery within the previous year¹.

Over the years scientists have used various methods to divide *S. aureus* (and MRSA) strains into epidemiologically related or clonal groups. The purpose was to use these groups to monitor issues such as an outbreak or the source of an infection. A very simple, rapid and inexpensive method used is the antibiogram. MRSA isolates can be easily compared based on their susceptibility to various antimicrobials. The main drawback with this method is that MRSA strains seem to vary in their susceptibility based on the local environment, so it is not useful as a sole typing method². One of the earliest methods used was bacteriophage typing. The staphylococcal strains were

grouped according to phage susceptibility (whether a certain phage was capable of lysing the bacterial cells). The main drawback with this method was that many of the strains were non-typable using this method³. Later, molecular methods such as pulsed field gel electrophoresis (PFGE) were developed. In PFGE the bacterial DNA is digested with a restriction enzyme that yields infrequent cuts, such as *smaI* which yields 15-20 fragments⁴. The digests produce bands on an agarose gel that are characterized according to migration patterns. Isolates with the same band pattern are considered to be the same strain; with a difference of one to three bands, closely related. Those with six or more band differences are considered to be unrelated. The number of groups varies with the bacteria population being tested⁵. A very popular current method is multilocus sequence typing (MLST). This method compares the DNA sequence of seven housekeeping genes (genes that are always present in a given species). Isolates that match in at least six of the seven gene sequences are placed in the same clonal complex (CC). Most MRSA strains belong to five such groups, CC5, CC8, CC22, CC30, and CC45¹. Another typing method that has led to a large database that is used worldwide is *spa* typing. This method uses sequencing of only a single gene sequence from what is known as the X-region of the *S. aureus* protein A (*spa*) gene⁶.

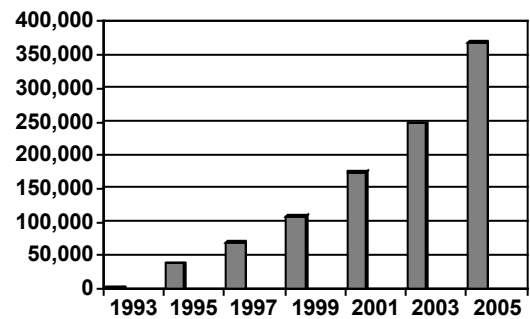
Another way that MRSA strains have been classified is by the structural makeup of the genetic element that confers the resistance to methicillin; the staphylococcal cassette chromosome *mec* (SCC*mec*). By comparing the structures of the SCC*mec* element from numerous MRSA strains, five group types have been described: SCC*mec* I to V. Most HA-MRSA strains have SCC*mec* types I, II, or III. Most CA-MRSA strains have SCC*mec* type IV, and there are also some with type V⁷. There will be a more in depth discussion of this topic in an accompanying paper (*Methicillin-Resistant Staphylococcus aureus: Molecular Aspects of Antimicrobial Resistance and Virulence*).

In 2003 the CDC developed a typing database for MRSA isolates from the U.S. They developed a PFGE-based typing system which was validated with MLST and *spa* typing data. The result established eight typing clusters designated as pulsed-field types (PFTs) USA100 through USA800. They found that PFTs USA100, -200, -500, -600, and -800 contained isolates that came mostly from HA-MRSA infections, while PFTs USA300 and -400 came mostly from CA-MRSA infections. USA700 isolates came from both CA- and HA-MRSA infections⁸.

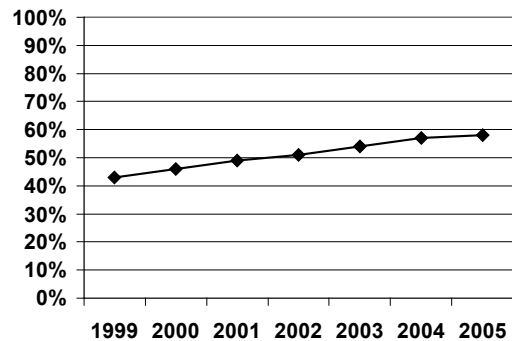
Various studies have been conducted in the last few years to determine the extent of CA- vs. HA-MRSA infections in the US. Most of these studies agreed that there were discernable differences between the two. In general, CA-MRSA patients

Figure 1.

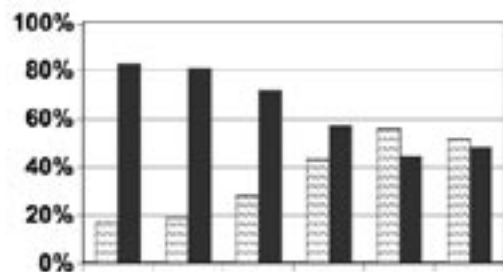
A. Number of MRSA infections in the U.S. 1993-2005¹⁷



B. Percentage of MRSA isolates to total number of *S. aureus* infections in the U.S. 1999-2005¹⁸



C. Percentage of CA-MRSA vs. HA-MRSA infections in Los Angeles 1999-2004¹⁰



tended to be very young, the types of clinical infections were different. CA-MRSA strains were mostly skin and soft tissue infections; pneumonia, bacteremia, endocarditis, osteomyelitis and toxic shock syndrome were more likely to be from HA-MRSA. The CA-MRSA strains were more likely to be susceptible to multiple classes of antimicrobials^{9, 10, 11, 12, 13}. These data suggest that the CA- and HA-MRSA strains developed independent of each other. There is some speculation that since CA-MRSA strains seem to resemble methicillin-susceptible *S. aureus* (MSSA) strains more than HA-MRSA strains, that CA-MRSA strains may have originally been MSSA strains that acquired SCCmec elements and became methicillin-resistant¹⁴.

An important observation is the fact that along with an increase in the percentage of *S. aureus* infections in the U.S. that are caused by MRSA strains, the percentage of CA-MRSA in relation to the total number of MRSA-caused infections has also been increasing in the U.S. (Fig. 1), and CA-MRSA strains have now invaded health care facilities and are being transmitted nosocomially among people in the same manner as HA-MRSA^{15, 16}.

The various studies have also produced some other interesting data on the geographical distribution of MRSA in the US. Although overall there seems to be a relatively uniform distribution, there is still evidence of a regional pattern of distribution (Fig. 2).

Because of the growing threat of MRSA, there have been governmentally initiated programs to educate the public and members of the healthcare community, and directives on how to manage this threat. The Institute for Healthcare

Improvement (IHI) developed a campaign, *Protecting 5 Million Lives From Harm*, that made reducing MRSA infections one of its six initiatives. The campaign covered a two-year span from December 2006 to December 2008. The MRSA goal was to be met by educating healthcare workers and by implementation of proven infection control practices²¹.

Also at this same time, the Association for Professionals in Infection Control & Epidemiology (APIC) conducted a survey of U.S. healthcare facilities about the prevalence of MRSA. The survey was conducted in October and November of 2006. The results were released in March 2007 along with guidelines for MRSA management, the *Guide to the Elimination of Methicillin-Resistant Staphylococcus aureus (MRSA) Transmission in Hospital Settings*²². This is a comprehensive guide that includes: risk assessment, a surveillance program, hand hygiene guidelines, contact precautions, environmental and equipment cleaning and decontamination, and targeted active surveillance cultures. These surveillance guidelines, along with a report from the Society for Healthcare Epidemiology of America (SHEA) which recommends testing of high-risk groups, have led to some states implementing mandatory screening of these patients at admission to the hospital^{23, 24}; to some hospitals wanting to test all patients before admission; and to some wanting to also test all of their workers. Although it could prove useful to identify every carrier of MRSA in the US, and know the types of all these strains, the reality is that it could prove to be a financial and staffing hardship for many clinical labs. There is also the issue of what type of specimen should be collected, with the validity of using nasal swabs alone or swabs from multiple additional sites, such as axillary and rectal cultures^{17, 25}.

The admission screening studies for high-risk patients that have been done show mixed results. Some didn't see a real reduction in MRSA²⁶, and others did²⁷. Since successful eradication of MRSA entails implementing the proper isolation protocols, it is no surprise that the Robicsek study, done at a facility that used real-time PCR for rapid detection of MRSA (which gives a quick turn-around time so that isolation protocols can be put into place within 24 hours), had better success than the West study that used cultures for MRSA identification (which meant a turn-around time of 48 hours or more). Because real-time PCR testing is much more costly, effective eradication of MRSA using admission screening techniques is directly tied to the financial status of the laboratory doing the tests.

Figure 2. Percentage of *S. aureus* infections in the U.S. caused by MRSA as of 200519, 20



The shift in prevalence of CA-MRSA versus HA-MRSA, and the recent serious outbreaks among a new high-risk group, which is usually thought to be extremely healthy, young adult athletes²⁸, means that it is imperative to discover MRSA carriers in the general population as well, before this new-age epidemic is out of control. Whether or not we can procure the financial resources to achieve screening regimens remains to be seen, but those who work in the laboratory can expect that a large part of the workload in the Micro department may soon be for MRSA identification.

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