

Epidemic Community-Associated Methicillin-Resistant *Staphylococcus aureus*

Modern Times for an Ancient Pathogen

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Staphylococcus aureus is an important pediatric pathogen causing community-acquired and nosocomial infections. Methicillin-resistant *S. aureus* (MRSA) isolates were long recognized as health care-associated pathogens (HA-MRSA) found in patients frequenting hospitals and long term care facilities. However, the recent recognition of MRSA infections in healthy children with no risk factors for MRSA signaled that MRSA epidemiology has undergone an important change.¹ New community-associated MRSA (CA-MRSA) strains have been responsible for well-recognized *S. aureus* infectious syndromes such as skin and soft tissue infections and “new” syndromes such as necrotizing pneumonia, necrotizing fasciitis, septic thrombophlebitis and severe sepsis.² In the first reports describing CA-MRSA isolates, it was recognized that they were less resistant to non- β -lactam antibiotics than HA-MRSA. Further, CA-MRSA clinical syndromes differed from those caused by HA-MRSA and more often resembled community-acquired methicillin-susceptible *S. aureus* (CA-MSSA) disease.³

What does the term CA-MRSA mean? Definitions have varied. The Cen-

ters for Disease Control and Prevention has defined CA-MRSA as an isolate obtained from a patient in the outpatient setting or in the first 48 hours of hospitalization in the absence of identified risk factors for MRSA acquisition. Others have relied on the antibiotic resistance profile, usually referring to clindamycin susceptibility to define CA-MRSA isolates. A molecular definition exploits certain genetic polymorphisms present among MRSA strains.

MOLECULAR CHARACTERISTICS OF MRSA

The *mecA* gene confers methicillin resistance by encoding penicillin-binding protein 2a (PBP2a), an enzyme with decreased affinity for β -lactam antimicrobials. PBP2a and native PBP2 work in concert to allow cell wall synthesis despite the presence of β -lactam antibiotics, thus effectively conferring resistance to penicillins, cephalosporins and carbapenems. The *mecA* gene is contained within a mobile genetic element called the staphylococcal chromosome cassette *mec*, or SCC*mec*. This element integrates into the *S. aureus* genome at a site-specific location adjacent to a gene called *orfX*. SCC*mec* elements contain a *mec* complex and a *ccr* complex. The former consists of the *mecA* structural gene and its variably present regulatory elements *mecI* and *mecRI*. The *ccr* complex contains *ccr* genes that mediate insertion and excision of SCC*mec* from the bacterial genome. Genetic polymorphisms in the *ccr* and *mec* complexes allow the classification of SCC*mec* elements into 5 allotypes, designated SCC*mec* types I–V.

In the original description of SCC*mec* elements,⁴ HA-MRSA strains were found to contain SCC*mec* types I, II and III; type II is now the most prevalent of these in U.S. HA-MRSA strains.⁵ The sequence of a type II SCC*mec* element revealed transposons and integrated plasmids that mediate resistance to non- β -lactam antibiotics, explaining in part the phenotype of multidrug resistance among HA-MRSA strains.

In contrast, CA-MRSA strains were found to contain SCC*mec* element types IV and V.^{6–8} Both elements lack antibiotic resistance genes other than *mecA*, thereby explaining the tendency toward resistance to only β -lactams in CA-MRSA strains.

The variable presence of genes encoding resistance to macrolides, lincosamides and streptogramins has provided the basis for use of clindamycin susceptibility as a marker for CA-MRSA strains. Transposon 554 (Tn554) found in SCC*mec* type II elements contains the *erm* gene that confers erythromycin resistance. *erm* also confers constitutive or inducible resistance to lincosamides such as clindamycin and streptogramin B. Isolates containing *erm* express the so-called MLS_B resistance phenotype. Thus HA-MRSA strains containing SCC*mec* type II are typically resistant to β -lactams as well as erythromycin and clindamycin (and streptogramin B). Antibiotic pressure in the hospital has selected for strains that have acquired resistance to other non- β -lactam antimicrobials; the genes responsible for these resistance determinants may be present within the SCC*mec* element, on plas-

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mids or elsewhere in the bacterial genome.

SCC*mec* types IV and V, found in most CA-MRSA strains, do not contain Tn554 or *erm* and, thus, many are susceptible to erythromycin and clindamycin. However, *erm* may be present on a plasmid or elsewhere in the genome. It is also possible that *msrA*⁹ or other genes conferring resistance to macrolides may be present in a CA-MRSA strain. *MsrA* encodes an efflux pump specific to macrolide antimicrobials. When erythromycin resistance is mediated by *msrA*, inducible resistance to clindamycin does not occur.

Performance of the "D test" by microbiology laboratories is necessary to detect inducible resistance to clindamycin in MRSA isolates that test resistant to erythromycin but susceptible to clindamycin. In this test a D-shaped zone of inhibition appears around the clindamycin disk when the erythromycin disk is placed nearby if erythromycin-induced clindamycin resistance is elicited. A positive D test signals that treatment failure may result if clindamycin is used.

SPREAD OF CA-MRSA

The differing size of the SCC*mec* element types probably plays a role in their mobility. Although the mechanism of cell to cell transfer of the SCC*mec* elements has not been elucidated, types I–III are believed to be too large for frequent transfer between strains. However, the smaller and presumably more mobile SCC*mec* IV and V elements are believed to be more easily translocatable between strains.² This observation is supported by molecular techniques such as pulsed field gel electrophoresis or multilocus sequence typing that indicate that SCC*mec* types IV and V are present in multiple *S. aureus* genetic backgrounds. Translocation of SCC*mec* IV and V is believed to be frequent with the resultant MRSA clones surviving on the basis of ecologic and pathogenic fitness.

CA-MRSA DISEASE

The similarity in disease presentation of CA-MRSA and CA-MSSA compared with HA-MRSA may reflect the expression of different toxin genes. A comparison of CA-MRSA and HA-MRSA strains revealed that 7 exotoxin genes were more likely to be found in CA-MRSA strains.¹⁰ These included *lukS-PV*, *lukF-PV*, *sea*, *seb*, *sec*, *seh* and *sek*. It is not known which, if any, of the toxins mediate clinical disease, although considerable attention has been focused on Panton-Valentine leukocidin (PVL).

Infections caused by CA-MRSA are often characterized by tissue necrosis. More than 90% of CA-MRSA disease-causing strains bear the genes encoding PVL, a pore-forming cytolytic toxin shown to have specificity for leukocytes.¹¹ PVL is encoded by 2 genes, *lukS-PV* and *lukF-PV*, that can be transferred between strains by bacteriophage. Lysis of polymorphonuclear leukocytes by PVL can initiate the release of inflammatory mediators. Although PVL was present in <5% of unselected *S. aureus* strains, it is present in most MSSA strains responsible for furunculosis and necrotizing pneumonia and in nearly all CA-MRSA isolates.^{12,13} Few HA-MRSA strains produce PVL.

SCC*mec* types IV or V together with PVL are commonly regarded as molecular markers of CA-MRSA. Their presence is thought to confer a fitness advantage to CA-MRSA strains that allows them to survive and disseminate.

BURDEN OF CA-MRSA DISEASE

Outbreaks of CA-MRSA infections in sports teams, prisons and military units, as well as increasing numbers of emergency room visits and hospital admissions because of CA-MRSA infection point to the need for further control measures, prevention and treatment strategies. At Driscoll Children's Hospital in Corpus Christi, the incidence of infections caused by CA-MRSA increased from 9 in 1999 to

459 in 2003.¹⁴ Other centers are experiencing the same trend. Although the frequency of CA-MRSA asymptomatic colonization and infection still varies by geographic location, all practitioners must be aware of the increasing burden of disease due to CA-MRSA.

The distinction between HA-MRSA and CA-MRSA strains will become more difficult as HA-MRSA strains move into the community and CA-MRSA strains move into the hospital. The occurrence of bacteremia and septic shock due to CA-MRSA-type strains in a neonatal intensive care unit highlighted the fact that a community organism can become a serious nosocomial pathogen.¹⁵

Clinical decision making relies on recognition of staphylococcal syndromes, appropriate culturing and treatment based on clinical syndrome and antibiotic susceptibility.

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