

■ FEATURE

Resistant bacteria spread through US communities

70% of isolates are now resistant to all β -lactam antibiotics

Infections due to antibiotic-resistant strains of *Staphylococcus aureus* are rising sharply in some US communities. These organisms, called community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), are resistant to all β -lactam antibiotics, including commonly prescribed cephalosporins.

"We have now lost the most useful class of antistaphylococcal antibiotics for empirical therapy", says Henry Chambers, professor of medicine at the University of California at San Francisco and chief of the division of infectious diseases at San Francisco General Hospital.

CA-MRSA also seem to be more virulent than similarly resistant strains that reside in hospitals. They often infect healthy, young people who do not have typical risk factors, such as recent hospitalisation, chronic disease, immunosuppression, or recent antibiotic treatment.

Earlier this year, five people in Colorado, who were either members of a fencing team or lived with team members, developed CA-MRSA infections. Two required hospitalisation and received intravenous antibiotic therapy. Local health officials and investigators at the US Centers for Disease Control and Prevention (CDC) suspect the bacteria were spread among the team by the leads of an electronic sensor that fencers use to detect when they have been touched by their opponent's weapon.

According to the CDC, similar outbreaks have occurred among American football players and wrestlers. In autumn 2000, ten members of a Pennsylvania American football team developed CA-MRSA infections, seven of whom needed to be admitted to hospital. And, in autumn last year, two members of a college American football team in Los Angeles, California, were

hospitalised, with one requiring surgical debridement and skin grafting.

Outbreaks of CA-MRSA have also occurred among prison inmates, Native Americans living in rural communities, military recruits, and men who have sex with men. But apart from these sporadic reports, there is scant information on how widespread the problem is. "We don't have very good surveillance data to tell us how quickly it is spreading", says Todd Weber, who coordinates antimicrobial resistance activities for the CDC's National Center for Infectious Diseases (Atlanta). "But it's clearly out there", he adds.

Methicillin-resistant *S aureus* strains have been a major problem in hospitals worldwide for decades. Although the term suggests the MRSA strains are resistant only to methicillin, hospital strains are usually resistant to several antibiotics, including antibiotics from different drug classes. Roughly half of *S aureus* isolates in US hospitals are now MRSA, a growing proportion of these are sensitive only to vancomycin, and in recent years strains that are resistant even to vancomycin have appeared.

Although hospital MRSA strains appear in the community, the CA-MRSA strains seem to be different, says Weber. CA-MRSA have a number of distinguishing characteristics, the most significant of which is that their drug resistance is usually limited to the β -lactams and not drugs from other classes. "I think if you had asked people some years ago how resistant staph would enter the community, they would have guessed it would have come out of the hospitals. In fact, that does not appear to be the case here", says Weber.

Individual cases and outbreaks of CA-MRSA have been reported during the past 20 years, but the problem seems to have taken off relatively recently. In the late 1990s, Robert Daum, professor of paediatrics at the University of Chicago, and his co-workers at the University of Chicago's Children's Hospital were surprised to see a spate of MRSA infections in children with none of the usual risk factors. To investigate further, they compared the prevalence MRSA in their institution between 1988 and 1990 with the prevalence between 1993 and 1995. In children not considered at risk, community-acquired infections had risen from 10 cases per 100 000 admissions to 259 per 100 000—a 25-fold increase (*JAMA* 1998; **279**: 593–98).

In 1999, a report in the CDC's *Morbidity Mortality Weekly Report*

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Penicillin-resistant bacteria

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(MMWR) describing the deaths of four children from the midwestern states of Minnesota and North Dakota brought national attention to the problem.

All the patients had been initially treated with a cephalosporin antibiotic. All turned out to have MRSA isolates that were susceptible to all microbial agents—except β -lactams. None of the strains were similar to strains found in local hospitals. The children came from different races and from both urban and rural communities, which suggests that “MRSA colonisation may be widespread, especially in this region of the United States”, the CDC investigators wrote (*MMWR* 1999; **48**: 707–10).

The following year, Sheldon Kaplan and his co-workers at Texas Children’s Hospital in Houston started tracking community-associated *S aureus* isolates. “In the first month of our study, we documented that one-third of our *S aureus* isolates were resistant to methicillin”, says Kaplan, who is professor of paediatrics at Baylor College of Medicine and chief of the hospital’s infectious disease division. “By November, that proportion had increased to 50% and within 6 to 13 months it had gone up to 70%.”

Similar increases are being seen across of his state, Kaplan says. “Once it gets into a community, it looks like it spreads like wildfire. This appears in every group, every ethnicity. It doesn’t matter if it’s whites, blacks, or Hispanics. We’ve mapped this out on the zip-code maps of Houston, and it’s in every zip code. It’s all over.”

β -lactam antibiotics kill staphylococci by targeting bacterial enzymes, called penicillin-binding proteins, which are crucial to cell-wall synthesis. MRSA strains carry a gene called *mecA* that codes for an altered form of these proteins. β -lactam antibiotics have a low affinity for the altered form, so bacteria that express it can tolerate high concentrations of these drugs.

The *mecA* gene is found on mobile elements, called the staphylococcal cassette chromosome, that can pop in and out of the bacterium’s DNA. In hospital-acquired MRSA strains, these cassettes are relatively large, too large for them to jump easily from strain to strain. As a result, although these strains are found worldwide, all have emerged from a few clones. *MecA* in the hospital strains enables them to out-compete other strains in hospitals, where antibiotics are used frequently. The cost of maintaining these large

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Methicillin-resistant *Staphylococcus aureus*

cassettes, however, may also keep the hospital strains from thriving in the community where, because antibiotic use is less, resistance genes do not provide a great competitive advantage.

The *mecA* cassette found in the community-associated MRSA strains is much smaller than those in the hospital strains. It may therefore be less costly for the bacteria to maintain, enabling them to survive in the community. The smaller size also means the cassettes can jump from one strain to another, increasing the chance it will be

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introduced into a wide variety of *S aureus* strains, including more virulent ones.

Indeed, some researchers believe CA-MRSA may be more virulent than many strains they see. The fact that these bacteria are causing disease in healthy people in the community “suggests there are virulence determinants on the strain that facilitate both the spread of these strains and their ability to cause infections”, says Franklin Lowy, professor of medicine and pathology at Columbia College of Physicians and Surgeons (New York). One virulence gene associated with CA-MRSA is a leukocyte-killing toxin called Pantone-Valentine leukocidin. It seems to increase the strains’ ability to

infect the skin and soft tissues, but it is likely that other genes, such as those that improve adherence to skin, may explain CA-MRSA’s ability to spread in the community.

CDC officials are now trying to determine the true prevalence of CA-MRSA. The institute has awarded grants of US\$3 million to five research groups, including groups led by Lowy, Daum, and Chambers, to study the strains’ epidemiology, genetic characteristics, and how they cause disease. To prevent infections, the CDC is warning high-risk groups such as athletes—who often have abraded skin, frequent skin-to-skin contact, and who often share equipment—that they may be contaminated, urging them to improve hygiene, keep cuts and abrasions clean and covered, and to regularly clean equipment, linens, and other items that might be shared.

The recommended first-line therapy for skin and soft-tissue infections remains local care and incision, and drainage when necessary, says Daum. “But if antibiotic therapy is warranted, health-care providers now need to consider that an MRSA strain may be involved. There are still places where the CA-MRSA strains are not common”, Daum says. In those areas, health-care providers “can still use a β lactam for initial therapy”. But in places like Texas Children’s hospital, “we cannot do that anymore”, he says. “ β -lactams are gone.”

Michael McCarthy