CD SUMMARY

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only causes nasty infections but is also antibiotic-resistant; this appears to have happened repeatedly on different continents with SSC*mec*IV. In the US, a virulent strain of MSSA acquired *mecA* and began an infamous journey around the country under the alias USA300. High rates of skin and soft-tissue infection caused almost exclusively by MRSA have been described among in the incarcerated in Mississippi, Georgia, California, and Texas; Oregon clinicians in desmoteric[11] settings concur. Factors contributing to ongoing transmission in these settings include poor routine hygiene, behavioral and mental-health problems, inadequate laundering of clothes, poor wound care, and high medical staff turnover. The same strain of USA300 strain has also caused outbreaks in football players, wrestlers, and members of a fencing club. Does antibiotic resistance alone explain these outbreaks? Although it may explain poor response to empiric antimicrobials, the rapid spread of CA-MRSA across the world may be related to other factors such as toxins.

The diverse manifestations of *S. aureus* disease are related to the complement of toxins and virulence factors carried by each strain. Toxins include TSST-1 (toxic shock syndrome), enterotoxins (food poisoning among other effects), and the exfoliative toxins (scalded skin syndrome). A previously unpublicized exotoxin may be responsible for the frustration among clinicians and patients battling multiple, recurrent,

or necrotizing skin infections (often mistakenly called spider bites even in the absence of history of same). Panton-Valentine leucocidin (PVL), a synergohymenotropic[*] toxin, damages membranes of eukaryotic cells (especially neutrophils), kills tissue and impairs the immune response. First described in print over 70 years ago,[12] it is found in *nearly all* current CA-MRSA isolates but much less often in HA-MRSA or MSSA. PVL has been long associated with furunculosis (boils) and has now been linked to necrotizing skin infections and community-acquired necrotizing pneumonia. In March 2005, a Portland clinician presented two fatal cases of staphylococcal pneumonia in young adults at the weekly infectious disease conference. Although neither isolate was MRSA, both carried the PVL toxin gene. Virulence and antimicrobial resistance are not always linked: but they are in USA300. How does PVL contribute to transmission? Drainage from CA-MRSA, PVL-associated skin infections contaminates the environment, and staph can survive a week on a dry surface. These two factors likely facilitate the rapid spread of this organism, especially once it enters a closed, crowded, or brutish population.

SUMMARY

CA-MRSA has arrived in Oregon; empiric treatment with β-lactams for staphylococcal infection will not always be effective. Fluctuant lesions

should be drained and cultured to help clarify antibiotic treatment options. Outbreaks will occur; investigation provides an opportunity to identify groups at risk and new mechanisms of transmission. Ongoing surveillance such as that started in the Portland metro area will provide some rational basis for future recommendations. Without a vaccine, community-wide prevention is limited to common-sense recommendations about personal hygiene and sanitation.

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* This really is a word; syngergo—synergistic, two-component; hymenotropic—membrane-seeking.

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MRSA 2005: THE NEW NORMAL

Hospital epidemiologists and those caring for medical "frequent fliers" have grappled with MRSA for years; now nearly all providers encounter this pathogen, some with alarming regularity. Even state bureaucrats find their West Nile virus, hepatitis and salmonellosis work interrupted by concerns about MRSA from providers, the public, prison officials, and athletic groups. This variant, known as community-associated or CA-MRSA, is now established throughout Oregon. An update on epidemiology, drug resistance, diagnosis, treatment, and the challenges of prevention follow immediately; if you are still interested, the biology and vocabulary behind the story are next in the MRSA primer, pages 3 and 4.

STAPH COLONIZATION AND SPECTRUM OF DISEASE

Staphylococcus aureus is a bacterial pathogen afflicting people and animals from cradle to grave on every continent. Perhaps a third of humans are "colonized" by this bug on skin and mucosal surfaces, but most never become sick. Local infection follows direct invasion from a colonized surface, while bacteremia can lead to infection of virtually any organ or space. Osteomyelitis, septic arthritis, septicemia, endocarditis, pneumonia, and surgical-site or medical device infections occur regularly, sometimes with poor outcome. Food poisoning and toxic-shock syndrome illustrate disease caused by staphylococcal toxins.

WHAT IS CA-MRSA?

In the past, otherwise healthy people did not become infected with MRSA; those infected usually had what are now called "established risk factors" (ERFs), including:

- previous diagnosis of MRSA;
- hospitalization or long-term care; surgery; and
- dialysis or invasive devices such as intubations.

In the late 1990s, MRSA case series from Chicago[1] and several other sites in the US (but not Oregon) heralded a new era of staphylococcal resistance. Two features were striking; first, the afflicted, otherwise healthy people had no ERFs; second, the MRSA resistance was limited to β-lactams in sharp contrast to typical hospital isolates. In these reports, skin and soft-tissue infections among young patients predominated; their isolates were dubbed CA-MRSA for "community-associated" to distinguish them from those found in patients with established risk factors (now named HA-MRSA, for "healthcare-associated"). The spectrum of infections and outcome from CA-MRSA infections is similar to that of the familiar MSSA. And like MSSA infections, not all CA-MRSA infections are benign; the death of four mid-western children reported in 1999 demonstrated their virulence and the need for effective empiric therapy when serious staphylococcal infection is suspected.[2]

COMMUNITY ASSOCIATED MRSA EPIDEMIOLOGY

Many groups have been recent victims of CA-MRSA skin and soft-tissue infection outbreaks—including Native Alaskans, Native Americans, the homeless, injection drug users, men who have sex with men, inmates, military recruits, kids in childcare, post-partum women, and a variety of competitive athletes.[3] In 2003, 5 linemen and linebackers on the St. Louis Rams developed MRSA skin abscesses at the site of skin abrasions; in 3 players infection recurred.[4] Among the 58 members of the football team, playing lineman or linebacker and higher

body mass index were the only risk factors identified. Observations of practices and games showed that skin abrasions were common (2–3 per player per week), hand hygiene was poor, towels were shared, whirlpools were used without a preceding shower, and weight-training equipment was not cleaned routinely. After installation of soap dispensers, changes in wound care, and targeted antibiotics for MRSA, only one additional case occurred.

Analysis of most CA-MRSA outbreaks fails to reveal a single overriding factor; but close quarters, poor (often absent!) hygiene, skin disease and trauma are commonly observed. Control is most successful in settings where these factors are mutable.

Most CA-MRSA infections are not associated with an outbreak or a publicized risk group; and MRSA is not a nationally reportable disease, preventing a glib summary of its epidemiology. A large lab-based prospective study of MRSA in 2000 was recently reported from Minnesota.[5] Overall, 25% of staph isolates were MRSA, and 12% of these were CA-MRSA. Compared with HA-MRSA cases, those with CA-MRSA were much younger (23 vs. 68 years), more likely to be non-white and had lower incomes. Most CA-MRSA infections (75%) involved the skin, while respiratory and urinary tract infections were more common manifestations of HA-MRSA. Among CA-MRSA cases <18 years of age, only underlying skin disease (9%) was at all common; 85% of these younger patients had no underlying conditions. In contrast, most of those older than 18 had at least one risk factor such as smoking (19%), diabetes (17%), or preceding skin disease (13%). Most CA-MRSA isolates were susceptible to multiple antibiotics.

Proportions of MRSA in some regions are far higher than were seen in Minnesotans at the turn of the century. For example, at Texas Children's Hospital in Houston 74%, of community-associated staph infections are now MRSA.[6] In Oregon, CA-MRSA was anecdotally reported in the late 1990s but appears to have become widespread only more recently.
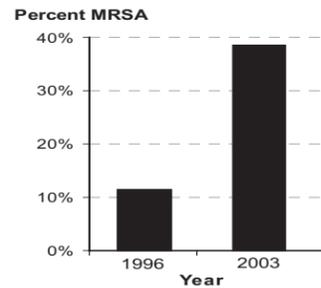
THE OREGON SITUATION

To clarify the regional situation and to contribute to a national effort we as part of our Emerging Infections Program began population- and laboratory-based surveillance for *invasive* MRSA (sterile-site cultures only—e.g., blood, joint fluid) in the Portland metropolitan tri-county area in January 2004. In just the first 9 months, labs reported 293 confirmed cases, of which 61 (21%) met the CA-MRSA definition (no ERFs). These isolates represent only the tip of the CA-MRSA iceberg since most disease is non invasive; our preliminary estimate of the rate of invasive CA-MRSA is 5 cases/100,000/yr.

Analysis of these fledgling data shows that the invasive CA-MRSA cases were much younger and more likely to be smokers or injection drug users compared with HA-MRSA cases, who more often suffered from diabetes, cardiac and renal disease. As expected, the percentage of isolates susceptible to clindamycin was much higher for CA-MRSA than for HA-MRSA.

Review of laboratory antibiotic resistance reports supports the rise of MRSA in the state. In 1996, a convenience sample of 18 Oregon microbiology laboratories from around the state showed that 11.5% of all *S. aureus* isolates tested (N=7,572) were MRSA; by 2003, a sample of 20 laboratories suggested that the proportion was three times as high (38.6% N=20,729), as depicted in the figure. Although the Portland metro area had the highest rate (44%), there was little variation among regions in Oregon.

The incarcerated are known to be at risk for CA-MRSA, and Oregon institutions have not been spared; an estimated 75% of staph isolated from Multnomah County inmates in 2004 were MRSA.

Percentage of MRSA among all *Staph aureus* isolates, Oregon 1996 vs. 2003

DIAGNOSIS OF MRSA

Optimal treatment of invasive staphylococcal infections requires culture of blood or potentially infected body fluids followed by antibiotic sensitivity testing. With less serious skin infections, culture of spontaneous or incision-induced drainage is encouraged to help customize therapy. In certain populations, such as the incarcerated, CA-MRSA is so common that culture is not always done. Pay careful attention to susceptibility testing results—particularly if the combination of clindamycin susceptibility and erythromycin resistance is reported; this may indicate *inducible* resistance, and the lab must do the so-called "D-test" to ensure clindamycin susceptibility. Another advantage of culture is detection of other pathogens, particularly *S. pyogenes* (a.k.a. group A *Streptococcus*), which can mimic *S. aureus* disease but may not be susceptible to agents used for CA-MRSA, particularly TMP-S and tetracyclines.

TREATMENT OPTIONS FOR CA-MRSA

With no clinical trials, no evidence-based recommendations can be made for treatment of CA-MRSA. Patients with suspected invasive staphylococcal infections requiring hospitalization now often receive empiric vancomycin; if methicillin-susceptible bugs are isolated, then β-lactams are preferred. Should empiric outpatient treatment for skin and soft-tissue infection be directed at MRSA? The answer depends on local microbiology results and clinical experience, but many Oregon clinicians now regularly encounter CA-MRSA. The list below has outpatient treatment recommendations for suspected CA-MRSA. A

very recent review discusses current and future choices for CA-MRSA therapy in more detail.[7]

Treatment recommendations
- Drain all fluctuant lesions (possibly adequate if afebrile and non-toxic)

Empiric oral agents:
- Trimethoprim-sulfamethoxazole
- Clindamycin
- Doxycycline
- Use Rifampin *only* in combination with one of the above.

INFECTION CONTROL AND PREVENTION

Currently, guidelines for MRSA in hospitals require contact isolation (gown, gloves, single room), but the high prevalence in some facilities makes this impractical. As MRSA becomes more prevalent, use common sense and standard precautions in outpatient areas.

Outpatient Infection Control
- Standard precautions for all encounters (e.g. gown and gloves while caring for ANY open wound)
- Hand hygiene by all healthcare staff before and after patient contact
- Disinfect examination areas surfaces and common-use equipment between uses
- Dispose of dressings appropriately

Home Infection Control
- Bathe using soap and water
- Cover wounds with clean dressings
- Avoid sharing potentially contaminated items with others

Measures for preventing staphylococcal skin infections among sports participants[8]
- Cover all wounds
- Encourage good hygiene
- Ensure availability of adequate soap and hot water
- Discourage sharing of towels and personal items
- Establish routine cleaning schedules for shared equipment
- Train athletes and coaches in first aid for wounds and in recognition of wounds that are potentially infected
- Encourage athletes to report skin lesions and coaches to assess athletes for skin lesions

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There is no vaccine available for *S. aureus,* nor is there consensus on the best bacterial target or the populations most needing protection. One experimental vaccine directed against the capsular polysaccharide showed modest efficacy of short duration (40 weeks) in adults with end-stage renal disease.[9]

DECOLONIZATION

Decolonization protocols for patients with recurrent infections have been proposed including nasal mupirocin, with or without concurrent systemic antibiotics, and bathing with chlorhexidine, povi-

!!! SPECIAL BONUS !!! MRSA PRIMER

done-iodine or dilute bleach. These measures should be considered on a case by case basis and are not routinely recommended since recolonization occurs frequently.

HISTORY

Unbelievable though it sounds today, Penicillin G was a great anti-staphylococcal antibiotic when first introduced for clinical use in the 1940s. The therapeutic honeymoon ended just a few years later, spurring development of new antibiotics developed specifically for staph infections. As with penicillin, resistance to the first of these new agents—methicillin—was reported shortly after its introduction into clinical use in the 1960s[10] giving birth to an abbreviation, MRSA, that has long outlived the drug. MRSA are resistant to all β-lactams (penicillins, cephalosporins and carbapenems), while MSSA (methicillin-sensi-

tive *S. aureus*) are susceptible to methicillin and current anti-staph β-lactams like oxacillin and cefazolin. These and other definitions are summarized in the Table.

For over 30 years, MRSA targeted patients in and around hospitals; treatment was a headache since MRSA was susceptible to few antibiotics, the most reliable being IV vancomycin. Since the late 1980s, VRE (vancomycin-resistant enterococci) have become established as a frequent, sometimes untreatable, nosocomial pathogens, especially among compromised hosts. Could nearly impossible-to-treat vancomycin-resistant *Staph aureus* (VRSA) emerge and then spread? Will this be even worse than CA-MRSA? The genes conferring vancomycin resistance have migrated from VRE to *S. aureus,* but only 4 times so far in the US, first in 2002 and most recently in February 2005. Vancomycin intermediate *S. aureus* (VISA) is only slightly more common; currently to date VISA and VRSA have been found only in those with chronic illness and prolonged use of antibiotics.

BIOLOGY OF STAPHYLOCOCCAL RESISTANCE

All β-lactam antibiotics work by inhibiting penicillin-binding proteins (PBPs), essential bacterial cell-wall cross-linking enzymes. In 1945, when strains of *S. aureus* first acquired a secreted β-lactamase that degrades penicillin, the value of this landmark drug began to dwindle; a decade later it was nearly worthless for hospital staph infections, although it could still be used for sporadic community disease

until the 1960s. Methicillin and its relatives (e.g., oxacillin, nafcillin, cefazolin), designed to resist this β-lactamase, remained effective for decades against penicillin-resistant *S. aureus;* but the first MRSA quickly appeared and then spread in hospitals.

In both CA- and HA-MRSA, a gene known as *mecA* encodes a novel penicillin-binding protein (PBP2a) not inhibited by anti-staphylococcal β-lactams. Understanding the susceptibility of CA- and HA-MRSA to other classes of antibiotics, however, requires looking deeper into bacterial genetics. The *mecA* gene (and its regulators *mecR* and *mecI*) is found in a mobile genetic element (a set of genes that can move from one location to another) known as the staphylococcal chromosomal cassette or SCC*mec*. The characterization of 5 distinct types of SCC*mec* helps explain the recent emergence and behavior of CA-MRSA. Virtually all contemporary HA-MRSA are SSC*mec* types II or III, the largest of the SCC elements known (53–67 kilobase pairs for genetics aficionados) with space aplenty for the other resistance genes that make MRSA treatment so difficult. In contrast, the SCC*mec*IV found in most CA-MRSA is about one-third as big, with little room for such genes. The small size of SSC*mec*IV may contribute to community spread of MRSA if it neither slows bacterial growth nor requires antibiotic selective pressure for maintenance.

A mobile gene carrying antibiotic resistance has frightening potential. If *mecA* jumps into an already virulent strain of MSSA, the new bacterium not

MRSA Abbreviation Decoder

β-lactam antibiotic	Structurally related antibiotics, including penicillins, cephalosporins, carbapenems, and monobatams; that inhibit bacterial cell-wall synthesis
β-lactamase	Secreted bacterial enzymes that disrupt and inactivate certain β-lactam antibiotics
Penicillin-binding proteins (PBPs)	Bacterial enzymes that cross-link cell wall components; essential for bacterial survival
MSSA	Methicillin-senstive *Staphylococcus aureus*
MRSA	Methicillin-resistant *Staphylococcus aureus*
CA-MRSA	Community-associated MRSA; usually MRSA in a patient without established risk factors (ERFs)
HA-MRSA	Hospital-associated MRSA, defined as MRSA among those with ERFs
mecA	Gene encoding PBP2a, which is NOT inhibited by methicillin (or any other β-lactam); present in *all* MRSA.
VRE, VRSA	Acronyms for vancomycin-resistant *Enterococcus* and *S. aureus*, respectively
SCC	Staphylococcal chromosomal cassette, the mobile DNA element; carries *mecA*
PVL	Panton-Valentine leucocidin, a toxin often carried by CA-MRSA; linked to furunculosis and necrotizing infections