Staphylococcus aureus: Methicillin-Susceptible S. aureus to Methicillin-Resistant S. aureus and Vancomycin-Resistant S. aureus

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The evolution of methicillin-resistant and vancomycin-resistant Staphylococcus aureus has demanded serious review of antimicrobial use and development of new agents and revised approaches to prevent and overcome drug resistance. Depending on local conditions and patient risk factors, empirical therapy of suspected S. aureus infection may require coverage of drug-resistant organisms with newer agents and novel antibiotic combinations. The question of treatment with inappropriate antibiotics raises grave concerns with regard to methicillin-resistant S. aureus selection, overgrowth, and increased virulence. Several strategies to reduce the nosocomial burden of resistance are suggested, including shortened hospital stays and outpatient parenteral antimicrobial therapy of the most serious infections.

Naturally occurring strains of methicillin-resistant Staphylococcus aureus (MRSA) were first reported from England in 1961 [1], not long after the introduction of semisynthetic penicillins. Within a decade, MRSA was reported in the United States, with 22 such strains isolated from 18 patients at Boston City Hospital [2], and by 1981, it had become endemic in virtually all US health care facilities [3, 4]. A meta-analysis of studies of S. aureus bacteremia that were published from January 1980 through December 2000 demonstrated significantly increased mortality associated with MRSA infection, compared with infection due to methicillin-susceptible S. aureus (MSSA) [5]. Data collected from July 2004 through December 2005 by the Active Bacterial Core surveillance network (the laboratory surveillance component of the Emerging Infections Program of the US Centers for Disease Control and Prevention [CDC]) showed an estimated rate of invasive MRSA infection (bloodstream or other sterile sites) of 31.8 case per 100,000 population [6]. This trend is associated with very high morbidity and mortality. According to one estimate of incidence rates of MRSA infection in 2005, among 5287 patients hospitalized with MRSA infection, there were 988 deaths [6]; on the basis of these data, an estimated 18,650 patients died of invasive MRSA infection in the United States in 2005 [7]. If accurate, this projection suggests that MRSA-associated deaths exceeded the total estimated number of deaths (17,011) attributable to HIV infection and AIDS in the United States in 2005 [8].

As the prevalence of MRSA strains has steadily increased in health care facilities (health care–associated [HA] MRSA), community-associated (CA) infections have become increasingly endemic in many parts of the world [9–11]. Primarily associated with skin and soft-tissue infections, CA-MRSA can also cause severe pulmonary infections, including pneumonia and empyema [12, 13], and osteomyelitis or septic arthritis, urinary infections, and bacteremia [13].

According to The Surveillance Network-USA, an electronic network that collects microbiology data from 300 clinical microbiology laboratories across the United States, rates of MRSA infection have steadily increased in the United States since 1998 and were still increasing as of March 2005 [14]. Inpatient (HA) and outpatient (CA) trends for MRSA during the period from 1998
through March 2005 were analyzed for each of the 9 regions of the US Census Bureau (Figure 1) [14].

HA-MRSA VERSUS CA-MRSA

Established risk factors for HA-MRSA infection include hospitalization during the previous year, recent surgical procedure, exposure to broad-spectrum antibiotics, residence in a long-term care facility, receipt of hemodialysis, indwelling percutaneous medical devices and catheters, and intravenous drug use [6,15]. However, MRSA infection has occurred in persons in the community without these risk factors [15]. In 1999, 4 fatal MRSA infections in previously healthy children without recent hospitalizations were reported by the CDC [15]. It was later determined that the 2-year-old sister of one patient, a 12-month-old boy, had been treated for an MRSA infection 3 weeks earlier.

CA-MRSA and HA-MRSA isolates have been found to be microbiologically distinct, suggesting that CA-MRSA did not originate from HA isolates that escaped from the hospital setting [24]; rather, CA-MRSA seems to have emerged de novo from established CA-MSSA isolates [25, 26]. According to a typing scheme established at the CDC, the majority of CA-MRSA infections are caused by 2 pulsed-field gel electrophoresis types (USA300 and USA400), whereas the predominant genotypes endemic in hospitals are USA100 and USA200 [27].

In addition to the genetic differences, the infections caused by CA-MRSA and HA-MRSA are generally different; the CA pathogen is most frequently associated with skin and soft tissue (abscesses, boils, and folliculitis), whereas pathogens acquired in health care facilities are more likely to infect the respiratory tract, bloodstream, urinary tract, and surgical sites. Moreover, although CA-MRSA is more frequently susceptible to non-β-lactam antibiotics (such as clindamycin, trimethoprim-sulfamethoxazole, and tetracycline), compared with HA-MRSA, it also tends to be more aggressive [26]. CA-MRSA can cause highly invasive, rapidly progressive, life-threatening infections, such as necrotizing pneumonia, severe sepsis, and necrotizing fasciitis [28–30]. Bloodstream infections due to MRSA USA300 isolates have been introduced in the hospital environment from the community. According to a study of MRSA in a major Atlanta hospital, this genotype accounted for 20% of all nosocomial and 28% of all HA-MRSA bloodstream infections at that institution [31]. CA-MRSA has emerged as an important cause of infections in hospital emergency departments [16, 17], intensive care units, and neonatal intensive care units [18, 19] and in athletic participants [20, 21], military recruits [22], and persons in prisons [23].

MSSA TO MRSA

Some of the increased virulence shown by CA-MRSA has been attributed to the fact that many CA organisms harbor genes (lukS-PV and lukF-PV) that encode the subunits of Panton-Valentine leukocidin (PVL) [27]. Van de Velde first designated this toxin as “substance leucocide” in 1894 because of its ability to lyse leukocytes [32]. PVL consists of 2 proteins that combine together as subunits to form the leukotoxin that was first as-

Figure 1. Inpatient (IP) and outpatient (OP) rates of methicillin-resistant Staphylococcus aureus infection, by US Census Bureau regions. Adapted from Styers D, Sheehan DJ, Hogan P, Sahm DF. Laboratory-based surveillance of current antimicrobial resistance patterns and trends among Staphylococcus aureus: 2005 status in the United States. Ann Clin Microbiol Antimicrob 2006;5:2 [14].
associated with skin and soft-tissue infection by Panton and Valentine in 1932 [32]. Subsequent identification of the pvl genes confirmed the association of PVL with both superficial and severe skin and soft-tissue infection and necrotizing pneumonia among CA-MRSA isolates [33, 34] and later among CA-MRSA organisms [35]. However, evidence of the precise role of PVL in CA-MRSA pathogenesis and virulence is limited, and some data have failed to show a clear difference between PVL-positive and PVL-negative isolates in their ability to lyse human polymorphonuclear leukocytes [26].

The currently accepted model to explain the origins of CA-MRSA suggests that a small cassette conferring methicillin resistance (such as SCC\textsubscript{mecc} IV or V) is independently integrated into the genomes of many different ancestral MSSA clones found in different geographic regions and that a few of the most evolutionarily successful have survived [26]. This model parallels the emergence and spread of HA-MRSA in the 1980s, except that, unlike the HA isolates, the CA organisms emerged carrying pvl genes (Figure 2) [26]. HA-MRSA usually carries large SCC\textsubscript{mecc} I, II, or III cassettes for methicillin resistance, which also confer non-\beta-lactam antibiotic resistance. The pvl genes of CA-MRSA, however, are associated with SCC\textsubscript{mecc} IV or V cassettes and not types I, II, or III.

**VANCOMYCIN-RESISTANT S. AUREUS (VRSA)**

Glycopeptides, particularly vancomycin, have been considered to be the drugs of choice for treating MRSA bacteremia and sepsis since the prevalence of that organism surged during the 1980s [36]. The high prevalence of MRSA infection has led to increased use of vancomycin in chronic and seriously ill patients and, in turn, to the emergence of multiple phenotypes with reduced susceptibility to glycopeptides [37]. For example, heterogeneous vancomycin-intermediate S. aureus (hVISA), defined as organisms with minimal inhibitory concentrations (MICs) of 1–2 \(\mu\)g/mL (but with a subpopulation of daughter cells with the ability to grow at 4 \(\mu\)g/mL), appears to precede the development of vancomycin-intermediate S. aureus (VISA), with MICs of 4–8 \(\mu\)g/mL. Finally, VRSA is defined as organisms with MICs \(\geq 16 \mu\)g/mL [37].

Since the first documented clinical infection due to hVISA was reported in Japan (in a patient with MRSA pneumonia unresponsive to vancomycin [38]), VISA infections have been reported in patients from the United States, Europe, and Asia [39]. The first documented infection caused by VRSA in the United States was reported by the Michigan Department of Community Health in 2002 [40, 41]. Since then, 8 additional cases have been confirmed by the CDC (1 case each from Pennsylvania and New York and 6 from Michigan) [42–49].

hVISA and VISA strains probably arose as a result of fundamental changes in the bacterial cell wall and in important metabolic pathways [50]. In at least 2 S. aureus strains, currently unexplained accelerated cell-wall synthesis is correlated with vancomycin trapping in the outer layers, making less vancomycin available for target molecules [48, 50–52]. On the other hand, VRSA is thought to arise in a different manner, with resistance probably resulting from acquisition of genetic material from enterococci [50, 53]. In vitro transfer of the van\textsubscript{A} resistance determination gene from vancomycin-resistant Enterococcus faecalis to S. aureus has been demonstrated [47, 53], and conjugative transfer from vancomycin-resistant E. faecalis has appeared to be the mechanism of resistance in at least 2 unrelated clinical isolates of VRSA [40, 41, 47].

Most infections with VISA or VRSA have occurred after prior long-term use of glycopeptide antibiotics and in patients with chronic illness, such as preexisting chronic renal failure, diabetes mellitus, or vascular compromise with devitalized tissue [54]. However, Brazilian investigators reported the presence of 4 coagulase-negative Staphylococcus strains with reduced susceptibilities to vancomycin in healthy carriers inside and outside a health care setting [55]. The isolates were obtained from saliva, indicating the potential for disseminated oral strains to colonize other body sites and other individuals. None of the isolates were found to carry the van\textsubscript{A}, van\textsubscript{B}, and van\textsubscript{C} gene according to polymerase chain reaction analysis, and their cell walls became thickened after culture in a medium containing vancomycin.

In this study, the 4 coagulase-negative Staphylococcus strains showed variable levels of resistance to several antimicrobial agents, including oxacillin, cephalothin, ceftriaxone, chloramphenicol, trimethoprim-sulfamethoxazole, amikacin, erythromycin, tetracycline, and quinupristin-dalfopristin [55]. For example, 2 isolates were oxacillin resistant, and 2 were not. Only the former produced \(\beta\)-lactamase. All 4 isolates showed unsta-

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**Figure 2.** Model for the emergence of Panton-Valentine leukocidin (PVL)–producing community-associated methicillin-resistant Staphylococcus aureus (MRSA). A methicillin-susceptible S. aureus (MSSA) strain is infected and lysogenized by a phage (phiSLT) that harbors the genes encoding the PVL. Then a methicillin-resistance cassette (SCC\textsubscript{mecc} IV, V, or V\textsubscript{\textprime}) carrying the meca gene is horizontally transferred into the pvl-positive MSSA strain and integrates into the genome distant from the phiSLT integration site. Adapted with permission from [26]. Copyright © 2007, Nature Publishing Group.
malleable heterogeneous resistance to vancomycin, with reversion to susceptible levels after 10 days of serial passage on a drug-free medium. However, exposure of the revertants to $4 \mu g$ of vancomycin/mL selected for vancomycin-resistant strains at very high frequencies after 10 days of serial passage. Thus, after dissemination, coagulase-negative Staphylococcus organisms may be susceptible to both oxacillin and vancomycin but can revert to resistance when reexposed to vancomycin.

**MANAGEMENT OF MRSA INFECTION**

**Empirical therapy.** Clinicians faced with the increasing number of outbreaks of HA-MRSA and CA-MRSA infections have a challenging clinical dilemma: because of the increasing resistance of Staphylococcus strains to methicillin, is it safe to begin empirical therapy with a β-lactam antibiotic, such as cefazolin or oxacillin, or should therapy against MRSA also be included? One approach is to use the presence or absence of risk factors for MRSA to determine the empirical regimen.

In brief, HA-MRSA is more likely to cause infection in patients exposed to health care settings, such as hospitals, nursing homes, and dialysis centers. On the other hand, CA-MRSA is more likely to cause infection in community-dwelling diabetics and injection drug users [56]. Many recent outbreaks of CA-MRSA infection have occurred in populations with few or none of these risk factors, but have affected athletes [20,21], prisoners [23], and healthy children [10, 57, 58]. These reports suggest that among patients with CA-MRSA infection, exposure to specific non–health care environments may increase the likelihood that the infection is caused by MRSA.

Prospective analysis of cultures of sample from 180 patients hospitalized with CA *S. aureus* infection revealed that 108 patients were infected with MRSA and 78 were infected with MSSA [56]. Infection with MRSA was associated with younger age; skin and/or soft-tissue infection; snorting and/or smoking illegal drugs; recent incarceration; lower comorbidity index; more frequent visits to bars, raves, and/or clubs; and higher frequency of laundering clothes in hot water. However, the sensitivity, specificity, predictive values, and likelihood ratios for these risk factors were very limited in their ability to distinguish patients with CA-MRSA infection from those with CA-MSSA infection. Therefore, according to the investigators, in areas where a significant proportion of patients hospitalized for CA *S. aureus* infection carry MRSA, contact isolation should be given to all patients with suspected CA *S. aureus* infection, and it is prudent to include MRSA coverage in empirical antibiotic regimens [56]. Similarly, a prospective study of patients presenting to emergency departments in 11 US cities found that MRSA was the most common identifiable cause of skin and soft-tissue infections (50% overall; range, 15%–74%), but the only factor that was significantly associated with isolation of MRSA, compared with MSSA, was the presence of abscess at enrollment [16]. These investigators also recommended modifying standard empirical therapy to provide MRSA coverage.

Thus, to date, there seem to be no reliable epidemiological or clinical risk factors to distinguish patients infected with MRSA, regardless of whether they are infected with CA-MRSA or HA-MRSA, from those infected with MSSA. However, the answer to the question posed above seems to be that, in areas where MRSA infection is endemic, empirical therapy for serious conditions should include one of the following agents known to be effective and Food and Drug Administration approved for treatment of specific infections due to MRSA: quinupristindalfopristin, linezolid, daptomycin, or tigecycline.

**Antibiotics and MRSA.** A recent review examined the association between MRSA and certain classes of antibiotics that encourage the overgrowth of organisms resistant to them [59]. Acquisition and subsequent overgrowth of MRSA are particularly associated with β-lactam and quinolone antibiotic use, allowing rapid proliferation of an organism that may have been merely colonizing the skin. This may lead to clinical infection and potential transmission to others. Moreover, inappropriate antibiotics not only encourage overgrowth with MRSA but may also enhance the organisms’ pathogenicity, apparently through molecular changes that facilitate mechanisms, such as quorum sensing, adhesion, phage mobilization, exotoxin production, intracellular persistence, and biofilm formation, thus increasing the severity of the infection [59]. Quorum sensing, for example, is a chemical signaling mechanism that allows bacteria to sense the density of its colony in a given location and to invade other areas when the population threatens to exhaust the available nutrition at the original site, thus promoting proliferation and, potentially, bacteremia if the colony gains access to the bloodstream [59]. By removing susceptible commensal bacteria, inappropriate or inadequate antibiotic therapy encourages MRSA growth and, thus, promotes the quorum-sensing process, which may lead to increased virulence [59].

Although much of the evidence of enhancement of staphylococcal transmission by antibiotic therapy is based on in vitro studies, hospitals in countries reporting higher antibiotic consumption tend to have higher rates of MRSA infection, as measured as the proportion of *S. aureus* isolates carried by hospital patients that are methicillin resistant [60]. Conversely, 14 hospitals in countries with very low incidences of MRSA infection, particularly Nordic countries, were reported to use the fewest antimicrobials in Europe [61].

**Hospitals and MRSA.** The hospital environment is known to encourage replacement of the resident strain in the carrier with a more resistant version soon after admission, which is possibly the result of exposure to antibiotics or to hospital flora [62, 63]. An extensive study of the epidemiology and time course of endemic MRSA infection in a 600-bed teaching hos-
pital revealed that the change from MSSA to MRSA occurred on the first day in the hospital, when patients were given cefazolin as presurgical prophylaxis [62]. It is unclear whether such a time course for the change from MSSA to MRSA would occur in nonsurgical patients given cefazolin. Under selective antibiotic pressure, colonizing flora changed within 24–48 h, and for patients remaining hospitalized, subsequent courses of third-generation cephalosporins further selected and amplified the colonizing MRSA population; the final phases of this process are use of vancomycin, leading to vancomycin-resistant Enterococcus faecium (VREF) infection in some patients. Adapted with permission from [62].

Such studies support the generally accepted idea that the use of antimicrobial agents is a powerful selective force that promotes the emergence of drug-resistant strains [65]. A number of strategies have been proposed to minimize the burden of resistance in hospitals, including reduction of use of all antimicrobial classes, increased use of prophylactic antimicrobials to reduce colonization, rotation of different antibiotic classes in a temporal sequence, and simultaneous use of different antimicrobials for different patients [66–71]. Additional recommendations for the prevention of transmission of drug-resistant organisms in the hospital are fairly universal and uncontroversial and include hand hygiene, use of contact precautions, decontamination of the environment, and active surveillance to identify carriers [72]. This supplement suggests another strategy to help reduce the burden of drug resistance in the patient: outpatient therapy, either initially or after brief stabilization in the hospital.

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