SUPPLEMENT ARTICLE

Methicillin-Resistant *Staphylococcus aureus*: An Evolving Pathogen

Martin E. Stryjewski[1] and G. Ralph Corey[2,3]

[1]Department of Medicine and Division of Infectious Diseases, Centro de Educación Médica e Investigaciones Clínicas "Norberto Quirno" (CEMIC), Buenos Aires, Argentina; and [2]Division of Infectious Diseases, Duke Clinical Research Institute, and [3]Duke University Medical Center, Durham, North Carolina

The horizontal transmission of methicillin resistance to *Staphylococcus aureus* (MRSA) in hospital and community settings, and growing prevalence of these strains, presents a significant clinical challenge to the management of serious infections worldwide. While infection control initiatives have stemmed the rising prevalence, MRSA remains a significant pathogen. More recently, evidence that MRSA is becoming resistant to glycopeptides and newer therapies raises concern about the use of these therapies in clinical practice. Vancomycin resistance has become evident in select clinical settings through rising MICs, growing awareness of heteroresistance, and emergence of intermediate-resistant and fully resistant strains. While resistance to linezolid and daptomycin remains low overall, point mutations leading to resistance have been described for linezolid, and horizontal transmission of *cfr*-mediated resistance to linezolid has been reported in clinical isolates. These resistance trends for newer therapies highlight the ongoing need for new and more potent antimicrobial therapies.

Staphylococcus has plagued man for centuries [1]. Although staphylococci were probably causing diseases such as the "incurable boils" described in the sixth plague of Egypt [2], these organisms were only first described and classified as *Staphylococcus* (from the Greek *staphylos* ["grape"] and *kokkos* ["berry" or "seed"]) in 1882 by the Scottish surgeon Sir Alexander Ogston [3]. Two years later a German physician, Friedrich J. Rosenbach, described 2 pigmented colonies of staphylococci and proposed the nomenclature *Staphylococcus albus* (Latin for "white") and *Staphylococcus aureus* (from the Latin *aurum* ["gold"]) [4]. Since that time, *S. aureus* has continued to surprise scientists and physicians while infecting and decimating millions of patients.

Correspondence: Martin E. Stryjewski, MD, MHS, Department of Internal Medicine and Division of Infectious Diseases, CEMIC, Las Heras 2939, 3rd floor, Department of Medicine, Ciudad Autonoma de Buenos Aires (1425) Buenos Aires, Argentina (stryj001@fibertel.com.ar).

Clinical Infectious Diseases 2014;58(S1):S10–9

DOI: 10.1093/cid/cit613

RESISTANCE TO BETA-LACTAMS AND THE ORIGIN OF MRSA

At the core of the success of *S. aureus* as a human pathogen is its versatility. As part of its adaptation in the antibiotic era, *S. aureus* has been able to evolve, acquiring resistance to nearly all antibiotics used to treat it. Resistance to penicillin was reported in 1942, only 1 year after the miraculous drug was introduced [5]. In the mid-1940s the mechanism of penicillin resistance based on an inducible beta-lactamase was revealed [6]. By the 1950s half or more of *S. aureus* strains in large hospitals were resistant to penicillin [7, 8]. In addition, *S. aureus* was able to develop resistance to the other available antibiotics such as erythromycin, streptomycin, and the tetracyclines [7, 9, 10]. Unfortunately, history soon repeated itself. Methicillin was introduced in 1959 to overcome penicillin resistance. However, methicillin-resistant *S. aureus* (MRSA) was reported only 2 years later [11].

The mechanism leading to methicillin resistance was finally identified in 1981 [12] and involved the expression of a transpeptidase (PBP2a) with reduced affinity

for all available beta-lactam agents, including penicillin. PBP2a transpeptidase is encoded by chromosomal gene *mecA*, located in a mobile genomic element known as the staphylococcal cassette chromosome (SCC), in this case SCC*mec* [13]. SCC*mec* elements are classified by a hierarchical system into types and subtypes [14, 15]; to date, 11 types of SCC*mec* have been identified.

Although the origin of MRSA is not fully understood, it is suspected that methicillin-susceptible *S. aureus* (MSSA) acquired the *mecA* gene through horizontal transfer from coagulase-negative staphylococci [16, 17]. Subsequent evidence indicates that major MRSA clones repeatedly arose from successful epidemic MSSA strains [18]. The presence of distantly related MRSA lineages indicates that a single ancestral clone was unlikely to have arisen from a common origin [18, 19]. Despite the fact that ancestral clones seem to have successful adaptation characteristics, isolates with ancestral genotypes have not been proven to be more frequently associated with human disease than colonizing isolates [20]. In addition to the ancestral inheritance, *S. aureus* from certain clonal complexes (eg, CC30 and CC5) seems to be more commonly associated with invasive disease [21]. In addition, other candidate genes (within and outside SCC*mec*) have been proposed to explain the association between *S. aureus* and invasive disease [22, 23]. While SCC*mec* is crucial for antibiotic resistance, there is no direct evidence that SCC*mec* plays a clear role in MRSA virulence.

EPIDEMIOLOGY OF MRSA

Resistance to methicillin was uncommon until the late 1960s, when a multidrug-resistant MRSA (eg, phage type 83A complex) emerged in Europe [10, 24, 25]. For unknown reasons, the incidence of this MRSA in human infections gradually declined [25, 26]. For nearly a decade following this decline, MRSA clones were infrequently encountered and limited primarily to major urban hospitals [27]. However, a successful expansion of MRSA, which began in the late 1970s, turned into a nonstop evolutionary journey. MRSA resistant to gentamicin emerged in Europe and the United States [28, 29], and a multidrug-resistant MRSA became epidemic in Australia [30]. In the late 1980s MRSA rates in teaching hospitals reached 14% in Australia [31], while in the United States they increased from 8% to 22% by the end of the decade [32]. At the same time, an epidemic clone (EMRSA), thought to have been imported from Australia, was propagating in the United Kingdom [33, 34], and soon all of Europe and the United States were seeing dramatic increases in MRSA infections [18]. To illustrate this expansion, MRSA comprised nearly 60% of *S. aureus* organisms isolated in US intensive care units (ICUs) in 2003 [35]. Similarly in Latin America, rates of MRSA surpassed 50% in over half of the countries [36], and a similar situation was observed in many institutions from the Asia-Pacific region [37].

Names of MRSA clones commonly refer to a specific pulse field gel electrophoresis pattern (eg, USA100), although they are further classified using other complementary techniques such as multilocus sequence typing (of 7 housekeeping genes), SCC*mec*, and spa type (variants of *S. aureus* classified according to protein A). For example, the MRSA clone belonging to multilocus sequence type 5, which carries SCC*mec* II and spa-type 002 (ST5-MRSA-II *t*-002), is widely known as the New York/Japan clone or USA100.

Remarkably, only a select few MRSA lineages were widely disseminated and responsible for the majority of MRSA infections. Molecular-based epidemiologic studies have shown that 5 major pandemic clones (Iberian, Brazilian, Hungarian, New York/Japan, and Pediatric) accounted for almost 70% of hospital MRSA isolates [38, 39]. In support of this observation, a recent European study determined that MRSA-causing invasive infections are less diverse than MSSA-causing invasive infections and that MRSA spa types have a predominant geographic distribution [40].

Interestingly, recent reports from the United States and the United Kingdom indicate that rates of selected MRSA infections have remained static or have decreased. A combined survey of the National Nosocomial Infections Surveillance system and its successor, the National Healthcare Safety Network, demonstrated that in a large group of US ICUs, the percentage of methicillin resistance in central line–associated bloodstream infections (CLABIs) due to *S. aureus* increased from 47.9% in 1997 to 64.5% in 2007 [41]. However, the incidence of CLABIs due to MRSA (infections/catheter days) decreased by almost 50% in these same ICUs during the study period. Similar decrements were observed for other CLABIs, including those associated with MSSA [41]. Another study, conducted in more than 9 million US military beneficiaries enrolled in the TRICARE program, indicated that annual rates of hospital-onset MRSA bacteremia decreased (from 0.7 per 100 000 person-years in 2005 to 0.4 per 100 000 person-years in 2010) [42]. Estimates indicate that the number of CLABIs in US ICUs decreased from 43 000 in 2001 to 18 000 in 2009, with reductions in infections due to *S. aureus* being more marked than those caused by other pathogens [43]. Taken together, these observations suggest that the reduced incidence in CLABIs due to MRSA has probably resulted more from careful, sterile central-line insertion and improved infection control practices than from a change in the organism itself.

Actions to reduce healthcare-associated infections need to be emphasized. In the United Kingdom (England and Wales) such actions have included better antibiotic selection, isolation of infected patients and use of gloves to treat them, decontamination with skin and nose treatment prior to surgery if

prescreening shows MRSA carriage, and improved handwashing hygiene. Implementation of these measures has helped reduce MRSA infections to a total of 1481 cases reported across the National Health Service between April 2010 and March 2011, representing a 50% reduction from cases reported in 2008 and 2009. Interestingly, UK death certificates citing MRSA peaked at 1652 in 2006 but declined over subsequent years to 485 in 2010 [44]. Despite these good signals, we need to recognize that MRSA is extremely versatile and that physicians will be navigating the turbulent waters of *S. aureus* infections for many years to come.

RESISTANCE TO GLYCOPEPTIDES AND NEW AGENTS

Vancomycin received US Food and Drug Administration approval in 1958 [45]. Unlike other antibiotics, MRSA took almost 40 years to develop even partial resistance to glycopeptides such as vancomycin. Clinical failures of this ponderous, slowly bactericidal agent in patients with MRSA infections have resulted in a reevaluation of vancomycin minimal inhibitory concentration (MIC) breakpoints. In 2006 the Clinical and Laboratory Standards Institute (CLSI) lowered the vancomycin MIC breakpoints for susceptibility from 4 μg/mL or less to 2 μg/mL or less for MRSA [46]. Despite this realignment, concerns remain about the historical decrement of MRSA susceptibility to glycopeptides. This phenomenon, named "MIC creep," has only been documented in selected centers [47, 48] (Figure 1).

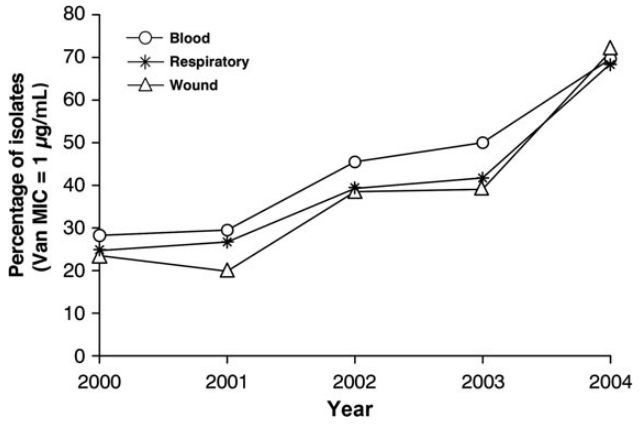

Figure 1. Percentage of *Staphylococcus aureus* isolates with vancomycin (Van) minimal inhibitory concentrations (MICs) of 1 μg/mL from blood, wound, and respiratory specimens from 2000 to 2004. Reproduced from: Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J Clin Microbiol **2006**; 44:3883–3886, with permission from the American Society for Microbiology.

Glycopeptide intermediate-susceptible *S. aureus* (GISA or VISA for this article; current MIC breakpoint between 4 and 8 μg/mL) was first described in Japan in 1996 [49] and involved a thicker cell wall with an excess of binding sites able to "trap" glycopeptides [50, 51] (Figure 2). This mechanism, which is not clonal, is commonly related to previous exposure to vancomycin [52]. Importantly, GISA isolates can return in vitro to vancomycin susceptible when the antibiotic pressure is removed [53]. Despite this, outbreaks of GISA already have been reported [54]. A recent study of 33 GISA strains obtained from the Network on Antimicrobial Resistance in *S. aureus* (NARSA) program indicates that GISA strains frequently carry SCC*mec* type II and are usually susceptible (>90%) to linezolid, telavancin, tigecycline, and minocycline [55]. Interestingly, not all GISA strains are MRSA, and a minority is susceptible to methicillin [55].

Although extremely uncommon, full vancomycin-resistant *S. aureus* (VRSA, current MIC breakpoint ≥16 μg/mL) emerged clinically in 2002 [56]. Unlike GISA strains, the mechanism of resistance in VRSA is due to acquisition of a *vanA* gene transferred from vancomycin-resistant enterococci [57]. To date, only 13 isolates of VRSA (8 from Michigan) are listed on the NARSA website [58]. These VRSA isolates were all susceptible to ceftaroline, daptomycin, linezolid, minocycline, and trimethoprim/sulfamethoxazole.

Soon after GISA was described, reports arose of vancomycin-susceptible strains of MRSA containing subpopulations resistant to glycopeptides (typically at a rate of 1 in 10^5 organisms) [59] not detected by conventional laboratory methods. These heteroVISA (hVISA) isolates represent an intermediary stage between fully vancomycin-susceptible *S. aureus* (VSSA) and GISA isolates. Patients with hVISA were commonly exposed to "low levels" of vancomycin (eg, <10 μg/mL) [60]. As a result, hVISA isolates have emerged from every lineage that has produced pandemic MRSA clones [18]. The reference method for identifying hVISA strains is the population analysis profile–area under the curve (PAP–AUC) calculation, which is labor intensive and not available in most laboratories. Given these difficulties, different screening methods to detect hVISA have been proposed [61]. Using these screening methods, most hVISA isolates have vancomycin MICs of 2 μg/mL or higher, but a minority will still have MICs <2 μg/mL [62]. Although the prevalence of hVISA (by reference method) seems to be low in the United States (eg, <1%) [63], there is some evidence that it is increasing in selected locations [64]. However, hVISA is more prevalent than originally thought in patients with invasive and difficult-to-treat MRSA infections. An international study found that 29% of patients with MRSA infective endocarditis had the hVISA phenotype [65]. This finding is in agreement with studies showing that most isolated hVISA came from bloodstream infections [64], although heteroresistance has also been found in patients with other invasive MRSA

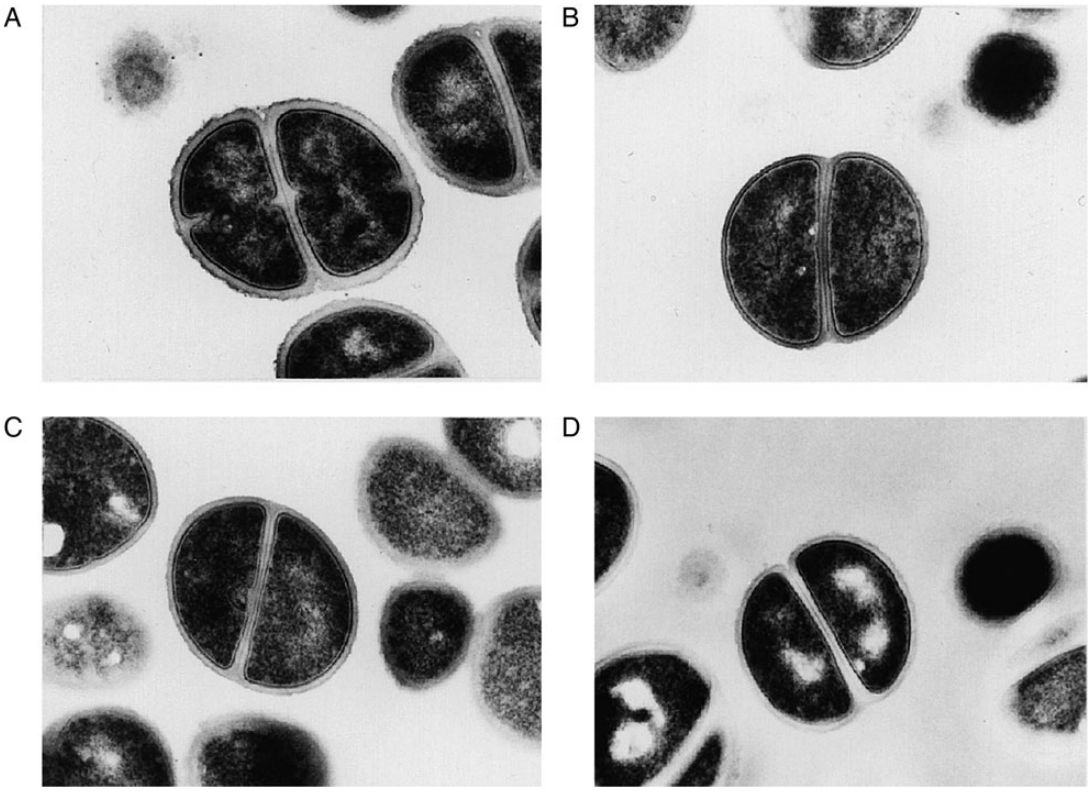

Figure 2. Transmission electron microscopy of (*A*) Mu50 (glycopeptide intermediate-susceptible *Staphylococcus aureus* [GISA]), (*B*) FDA209P (vancomycin- and methicillin-susceptible strain with vancomycin minimal inhibitory concentration (MIC) of 1 μg/mL), (*C*) H1 (methicillin-resistant *S. aureus* with vancomycin MIC of 2 μg/mL), and (*D*) Mu3 (heteroVISA). Notice the characteristic thickening of the cell was in the Mu50 (GISA) compared with other strains of *S. aureus*. Reproduced from: Hanaki H, Kuwahara-Arai K, Boyle-Vavra S, Daum RS, Labischinski H, Hiramatsu K. Activated cell-wall synthesis is associated with vancomycin resistance in methicillin-resistant *Staphylococcus aureus* clinical strains Mu3 and Mu50. J Antimicrob Chemother **1998**; 42:199–209, with permission from Oxford University Press.

infections [66]. Finally, an outbreak of hVISA has been recently described [67].

The mechanism of MRSA resistance to different antibacterials was elegantly reviewed by Lowy [68]. Table 1 displays the most common mechanisms of antibiotic resistance for *S. aureus*. Although uncommon, it is important to mention that MRSA resistance to new antibiotics such as linezolid or daptomycin has been described in clinical settings. Linezolid resistance associated with ribosomal point mutations in the 23S rRNA gene, or ribosomal proteins L3 and L4, have been associated with outbreaks of healthcare-associated linezolid-resistant infections in several countries [70]. Since pathogens susceptible to linezolid contain multiple rRNA genes, a cumulative threshold needs to be achieved before clinical resistance can be observed. More recently a plasmid-borne methyltransferase-mediated resistance mechanism *cfr* (for chloramphenicol-florfenicol resistance gene) has been identified; it conveys resistance to a range of antibiotics, including linezolid [70] (Figure 3). A recent outbreak of linezolid-resistant MRSA was reported in a Spanish ICU, mediated by the acquisition of *cfr* and associated with the extensive use of this antibiotic [73]. Resistance to daptomycin has also been described in a landmark bacteremia study [74]. Interestingly, several of these patients had incompletely drained infections. In addition, a US study showed a correlation between reduced susceptibility to vancomycin and daptomycin resistance, particularly in patients infected with MRSA demonstrating MICs to vancomycin of 4 μg/mL or greater [74]. From these data, it is clear that although new antibacterial agents are essential to treat this dynamic pathogen, it is equally important to understand and use these agents appropriately.

COMMUNITY-ASSOCIATED MRSA

Since the beginning of the MRSA expansion, infections due to this organism were primarily limited to major hospital centers and their healthcare systems. Community-acquired MRSA was rarely reported [75]. However, during the 1990s, a new epidemic of MRSA began. A unique clone of MRSA acquired in the

Table 1. Representative Mechanisms of *Staphylococcus aureus* Resistance to Selected Antimicrobials [68, 69]

Antibiotic	Resistance Gene(s)	Gene Product(s)	Mechanism(s) of Resistance	Location(s)
β-Lactams	*blaZ*	β-Lactamase	Enzymatic hydrolysis of β-lactam nucleus	Plasmid: Transposon
	mecA	PBP2a	Reduced affinity for PBP	Chromosome: SCC*mec*
Glycopeptides	GISA: unknown	Altered peptidoglycan	Trapping of vancomycin in the cell wall	Chromosome
	VRSA: *vanA*	D-Ala-D-Lac	Synthesis of dipeptide with reduced affinity for vancomycin	Plasmid: Transposon
Quinolones	*parC*	ParC (or GrlA) component of topoisomerase IV	Mutations in the QRDR region, reducing affinity of enzyme-DNA complex for quinolones	Chromosome
	gyrA or *gyrB*	GyrA or GyrB components of gyrase		
Aminoglycosides (eg, gentamycin)	Aminoglycoside-modifying enzymes (eg, *aac*, *aph*)	Acetyltransferase, phosphotransferase	Acetylating and/or phosphorylating enzymes modify aminoglycosides	Plasmid, Plasmid: Transposon
Trimethoprim-sulfamethoxazole (TMP-SMZ)	Sulfonamide: *sulA*	Dihydropteroate synthase	Overproduction of *p*-aminobenzoic acid by enzyme	Chromosome
	TMP: *dfrB*	DHFR	Reduced affinity for DHFR	
Tetracyclines	Tetracycline, doxycycline and minocycline: *tetM*	Ribosome protection protein	Binding to the ribosome and chasing the drug from its binding site	Plasmid: Transposon
	Tetracycline: *tetK*	Efflux protein	Efflux pump	Plasmid
Erythromycin	*msrA*	Efflux protein	Efflux pump	Plasmid
	erm (A, C)	Ribosomal methylase (constitutive or inducible)	Alteration of 23S rRNA	Plasmid: Transposons
Clindamycin	*erm (A, C)*	Ribosomal methylase (constitutive or inducible)	Alteration of 23S rRNA	Plasmid : Transposons
Linezolid[a]	*cfr*	Ribosomal methyltransferase	Methylation of the 23S rRNA that interferes with ribosomal binding	Plasmid
Daptomycin[b]	*mprF*	Lysylphosphatidylglycerol synthetase (LPG) synthetase	Increasing: synthesis of total LPG, outer LPG translocation and positive net charges on cell membrane	Chromosomal

Adapted with permission of the American Society for Clinical Investigation, from: Lowy FD. Antimicrobial resistance: the example of *Staphylococcus aureus*. J Clin Invest **2003**; 111: 1265–1273.

Abbreviations: DHFR, dihydrofolate reductase; GISA, glycopeptide-intermediate susceptible *Staphylococcus aureus*; LPG, lysylphosphatidylglycerol; QRDR, quinolone resistance–determining region; VRSA, vancomycin-resistant *S. aureus*.

[a] Other mechanisms for linezolid resistance involve mutations to the central loop of domain V of 23S rRNA or in the ribosomal proteins L3 and/or L4 of the peptide translocation center [70].

[b] Other mechanisms were also proposed, such as increased cell wall thickening, decreased membrane fluidity [71], and increased expression of *vraSR* [72].

community was first described in Western Australia [76]. A few years later, other community-acquired MRSA clones were recognized in Europe [77], the United States [78], Latin America [79], and Asia [80]. These clones often affected young people without healthcare contact, producing purulent skin infections [81] or pneumonia [82]. All these community-acquired MRSA strains differed from hospital strains of MRSA (eg, major MRSA pandemic clones). They were usually susceptible to multiple non–beta-lactam antibiotics and commonly carried SCC*mec* type IV (less commonly, type V) as well as genes for Panton–Valentine leukocidin (PVL).

Some of these new MRSA clones were extremely successful in displacing both emergent and endemic clones and spread geographically, infecting thousands. The clone USA400 (ST1-MRSA-IV, the first community-acquired MRSA clone in the United States), for example, was rapidly displaced by USA300 (ST8-MRSA-IV), which became the primary cause of purulent skin lesions in adults [83, 84]. Similarly, in France an emerging community-acquired MRSA clone, ST5 Geraldine, is now more prevalent than the previous clone, ST80 [85].

It was not long before community-acquired MRSA entered hospitals [86] and healthcare systems in the United States [87],

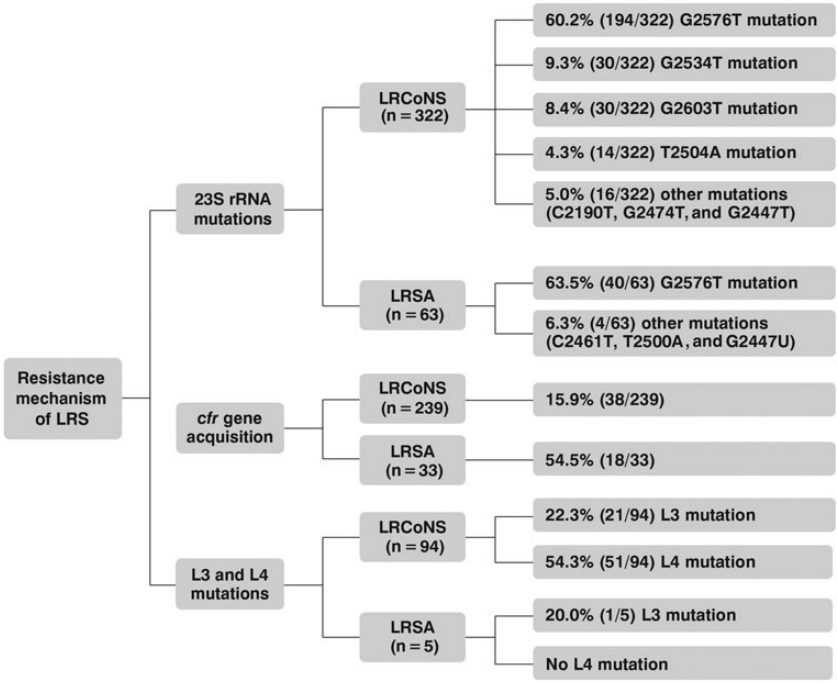

Figure 3. Currently known ribosomal point mutation (23S RNA/L3/L4) or plasmid-borne (*cfr*) mechanisms of resistance of linezolid-resistant *Staphylococcus* (LRS). The percentage of isolates that harbor each mechanism of linezolid resistance among the number of isolates tested for each mechanism is shown. Abbreviations: *cfr*, chloramphenicol-florfenicol resistance gene; LRCoNS, linezolid-resistant coagulase-negative *Staphylococcus*; LRSA, linezolid-resistant *Staphylococcus aureus*. Reproduced from: Gu B, Kelesidis T, Tsiodras S, Hindler J, Humphries RM. The emerging problem of linezolid-resistant Staphylococcus. J Antimicrob Chemother **2013**; 68:4–11, with permission from Oxford University Press.

causing invasive infections and making the "community-acquired" or "-associated" label less appropriate. A study of invasive MRSA infections in the United States determined that 16% of MRSA clones classified as hospital acquired were actually the USA300 clone, which originated in the community. In addition, a multidrug-resistant community-associated MRSA (USA300) has already been described in men who have sex with men [88]. VISA phenotype and resistance to daptomycin have also been reported in patients with infective endocarditis due to community-acquired MRSA (USA300) [89, 90]. Clearly, the epidemiology of community-associated MRSA reflects continuous changes in accord with the evolutionary nature of this pathogen [91, 92].

ANTIBIOTIC RESISTANCE AND VIRULENCE

Whether MRSA is more virulent than MSSA is still a matter of debate. Two metaanalyses have shown that patients with MRSA died more often than those with bloodstream infections due to MSSA [93, 94]. However, such differences might be explained by the fact that patients with MRSA infections were usually older, had more severe underlying disease, and often were receiving more inappropriate and/or suboptimal therapy than patients infected with MSSA. When carefully adjusted for other factors, MRSA was not associated with higher mortality in patients with VAP [95, 96]. To further confuse the issue, several investigators found that decreasing susceptibility to vancomycin within susceptible ranges was associated with worse clinical outcomes, particularly in patients with bloodstream infections [97–100] or pneumonia [66].

The link between reduced susceptibility and increased virulence remains unclear. Outcomes in patients with GISA infections have been poor [54], although this may be due to inappropriate treatment in otherwise sick individuals. Similarly, patients with bloodstream infections due to hVISA (bacteremia or endocarditis) had longer durations of bacteremia than patients with MRSA and without the hVISA phenotype [60, 65]. However, different studies did not find increased mortality in patients with bacteremia [101] or infective endocarditis [65] due to MRSA strains with the hVISA phenotype. In addition, 1 study reported higher survival in patients with bloodstream infections due to MRSA (mostly ST239) with the hVISA phenotype [102]. Thus the theories linking antibiotic resistance with either reduced fitness or increased virulence, although still attractive for hVISA, are unproven, and their clinical significance remains to be determined.

Other factors, such as the dysfunction of the accessory gene regulator (*agr*) may also play a role in MRSA virulence. The *agr* locus regulates expression of several virulence and housekeeping genes in a growth phase–dependent manner (quorum-sensing mechanism). Conceptually, increased expression of *agr* augments production of toxin and diminishes expression of surface cell adhesins [103]. Dysfunction in the *agr* locus was associated with reduced susceptibility to vancomycin [104], persistent MRSA bacteremia [105, 106], and, in 1 study, increased mortality [107].

As mentioned previously, community-associated MRSA usually carries marker genes (*luk-S* and *luk-F*) encoding for PVL. Different studies have suggested that PVL could play a major role in the virulence of community MRSA in both animal models [108] and humans [82, 108, 109]. However, these observations are not supported by large clinical studies. Bae and coworkers analyzed isolates obtained from 522 patients with complicated skin infections caused by MRSA who were enrolled in 2 clinical trials. Patients infected with MRSA strains carrying PVL-positive genes were significantly more likely to be cured than those infected with PVL-negative strains (91.6% vs 80.7%; $P = .015$) [110]. Similarly, PVL-positive USA300 was not associated with worse clinical outcomes in patients with bloodstream infections enrolled in a multinational trial [111]. Another study involving more than 100 patients demonstrated that HAP/VAP caused by PVL-positive strains of MRSA resulted in mortality equal to that caused by PVL-negative strains [112]. Similar findings were reported by Sharma-Kuinkel and colleagues in 287 patients with HAP/VAP (173 with MRSA) [113]. Thus, although PVL may have a role in virulence, an increasing body of evidence indicates that PVL is not a primary determinant of clinical outcomes in patients with community-acquired MRSA.

THE BURDEN OF DISEASE

Since first being identified, *S. aureus* infections have been associated with significant morbidity and mortality. In the preantibiotic era, bloodstream infections due to *S. aureus* yielded more than 80% mortality [114]. Although the prognosis has since improved, the impact of the disease remains dramatically high. Contemporary studies have shown that overall in-hospital mortality rates for patients with bloodstream infections due to MRSA are in the range of 30% [94, 115] but can be as high as 65% in some centers [115]. A study by the Centers for Disease Control and Prevention from 1999 to 2000 estimated that 125 969 hospitalizations for a diagnosis of MRSA infection occurred annually in the United States, including 31 440 for bloodstream infections and 29 823 for pneumonia [116]. More recent US estimates indicate MRSA causes approximately 95 000 invasive infections and 19 000 deaths per year [117]. This mortality number is higher than the rates of death produced by human immunodeficiency virus, viral hepatitis, tuberculosis, and influenza combined [118].

CONCLUSIONS

MRSA is a versatile, well-equipped pathogen with the potential to evolve and adapt to its host as well as to the treatments developed to control its invasive damage. Clearly, new therapies are needed in the ongoing struggle. In addition, prevention and rapid identification are essential. Determining the optimal methods of treating this evolving organism will require that both clinicians and researchers understand the organism, the patients, and the antibacterials being employed more clearly.

Notes

Supplement sponsorship. This article was published as part of a supplement titled "Tedizolid: A Novel Oxazolidinone for Gram-positive Infections," funded by Cubist Pharmaceuticals.

Potential conflicts of interest. M. E. S. has received payment for writing or reviewing this manuscript from Cubist Pharmaceuticals and for manuscript preparation from Cempra and has served as a consultant to Cerexa, Furiex, The Medicines Company, PRA International, Theravance, Trius Therapeutics, Nabriva, and Cempra. G. R. C. has served as a consultant to Merck, AstraZenica, Astellas, Cempra, Cubist Pharmaceuticals, Cerexa/Forest Pharmaceuticals, Furiex, PRA International, Inimex, Pfizer, GlaxoSmithKline, Polymedix, Achaogen, Trius Therapeutics, Rib-X, Nabriva, Seachaid, BioCryst, Durata, and Gilead. His institution has received grant funding from Theravance, The Medicines Company, and Innocoll.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed

References

1. Kloos WE. Taxonomy and systematic of staphylococci indigenous to humans. In: Crossley KB, Archer GL, eds. The staphylococci in human disease. New York City: Churchill Livingstone, **1997**:113–37.
2. Exodus 9:8-12 (ESV).
3. Wilson LG. The early recognition of streptococci as causes of disease. Med Hist **1987**; 31:403–14.
4. Rosenbach FJ. Microorganisms in the wound infections diseases of man. Wiesbaden, Germany: J.F. Bergmann, **1884**:18.
5. Rammelkamp M. Resistances of *Staphylococcus aureus* to the action of penicillin. Proc Soc Exp Biol Med **1942**; 51:386–9.
6. Bondi A Jr, Dietz CC. Penicillin resistant staphylococci. Proc Soc Exp Biol Med **1945**; 60:55–8.
7. Finland M. Emergence of antibiotic-resistant bacteria. N Engl J Med **1955**; 253: 909–22; contd.
8. Barber M, Rozwadowska-Dowzenko M. Infection by penicillin-resistant staphylococci. Lancet **1948**; 2:641–4.
9. Brumfitt W, Hamilton-Miller J. Methicillin-resistant *Staphylococcus aureus*. N Engl J Med **1989**; 320:1188–96.
10. Jessen O, Rosendal K, Bulow P, Faber V, Eriksen KR. Changing staphylococci and staphylococcal infections. A ten-year study of bacteria and cases of bacteremia. N Engl J Med **1969**; 281:627–35.
11. Jevons MP. "Celbenin"-resistant staphylococci [letter]. Br Med J **1961**; 1:124–5.
12. Hartman B, Tomasz A. Altered penicillin-binding proteins in methicillin-resistant strains of *Staphylococcus aureus*. Antimicrob Agents Chemother **1981**; 19:726–35.

13. Katayama Y, Ito T, Hiramatsu K. A new class of genetic element, *Staphylococcus* cassette chromosome *mec*, encodes methicillin resistance in *Staphylococcus aureus*. Antimicrob Agents Chemother **2000**; 44:1549–55.
14. Classification of staphylococcal cassette chromosome *mec* (SCC*mec*): guidelines for reporting novel SCC*mec* elements. Antimicrob Agents Chemother **2009**; 53:4961–67.
15. International Working Group on the Staphylococcal Cassette Chromosome Elements. Currently identified SCC*mec* types in *S. aureus* strains. Available at: http://www.sccmec.org/Pages/SCC_TypesEN.html. Accessed 13 November 2012.
16. Wu S, Piscitelli C, de Lencastre H, Tomasz A. Tracking the evolutionary origin of the methicillin resistance gene: cloning and sequencing of a homologue of mecA from a methicillin susceptible strain of *Staphylococcus sciuri*. Microb Drug Resist **1996**; 2:435–41.
17. Wielders CL, Vriens MR, Brisse S, et al. In-vivo transfer of mecA DNA to *Staphylococcus aureus* [corrected]. Lancet **2001**; 357: 1674–5.
18. Enright MC, Robinson DA, Randle G, Feil EJ, Grundmann H, Spratt BG. The evolutionary history of methicillin-resistant *Staphylococcus aureus* (MRSA). Proc Natl Acad Sci U S A **2002**; 99:7687–92.
19. Musser JM, Kapur V. Clonal analysis of methicillin-resistant *Staphylococcus aureus* strains from intercontinental sources: association of the *mec* gene with divergent phylogenetic lineages implies dissemination by horizontal transfer and recombination. J Clin Microbiol **1992**; 30:2058–63.
20. Day NP, Moore CE, Enright MC, et al. Retraction. Science **2002**; 295:971.
21. Fowler VG Jr, Nelson CL, McIntyre LM, et al. Potential associations between hematogenous complications and bacterial genotype in *Staphylococcus aureus* infection. J Infect Dis **2007**; 196:738–47.
22. Gill SR, McIntyre LM, Nelson CL, et al. Potential associations between severity of infection and the presence of virulence-associated genes in clinical strains of *Staphylococcus aureus*. PLoS One **2011**; 6: e18673.
23. Peacock SJ, Moore CE, Justice A, et al. Virulent combinations of adhesin and toxin genes in natural populations of *Staphylococcus aureus*. Infect Immun **2002**; 70:4987–96.
24. Benner EJ, Kayser FH. Growing clinical significance of methicillin-resistant *Staphylococcus aureus*. Lancet **1968**; 2:741–4.
25. Grundmann H, Aires-de-Sousa M, Boyce J, Tiemersma E. Emergence and resurgence of meticillin-resistant *Staphylococcus aureus* as a public-health threat. Lancet **2006**; 368:874–85.
26. Kayser FH. Methicillin-resistant staphylococci 1965-75. Lancet **1975**; 2:650–53.
27. Blackwell CC, Feingold DS. Frequency and some properties of clinical isolates of methicillin-resistant *Staphylococcus aureus*. Am J Clin Pathol **1975**; 64:372–7.
28. Cafferkey MT, Hone R, Coleman D, et al. Methicillin-resistant *Staphylococcus aureus* in Dublin 1971-84. Lancet **1985**; 2:705–8.
29. Keane CT, Cafferkey MT. Re-emergence of methicillin-resistant *Staphylococcus aureus* causing severe infection. J Infect **1984**; 9:6–16.
30. Pavillard R, Harvey K, Douglas D, et al. Epidemic of hospital-acquired infection due to methicillin-resistant *Staphylococcus aureus* in major Victorian hospitals. Med J Aust **1982**; 1:451–4.
31. Turnidge J, Lawson P, Munro R, Benn R. A national survey of antimicrobial resistance in *Staphylococcus aureus* in Australian teaching hospitals. Med J Aust **1989**; 150:65, 69–72.
32. Wenzel RP, Nettleman MD, Jones RN, Pfaller MA. Methicillin-resistant *Staphylococcus aureus*: implications for the 1990s and effective control measures. Am J Med **1991**; 91:221S–7S.
33. Mackintosh CA, Marples RR, Kerr GE, Bannister BA. Surveillance of methicillin-resistant *Staphylococcus aureus* in England and Wales, 1986–1990. J Hosp Infect **1991**; 18:279–92.
34. Cookson BD, Phillips I. Epidemic methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother **1988**; 21 (Suppl C):57–65.
35. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control **2004**; 32:470–85.
36. Guzman-Blanco M, Mejia C, Isturiz R, et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) in Latin America. Int J Antimicrob Agents **2009**; 34:304–8.
37. Bell JM, Turnidge JD, SENTRY APAC. High prevalence of oxacillin-resistant *Staphylococcus aureus* isolates from hospitalized patients in Asia-Pacific and South Africa: results from SENTRY antimicrobial surveillance program, 1998–1999. Antimicrob Agents Chemother **2002**; 46:879–81.
38. de Lencastre H, Oliveira D, Tomasz A. Antibiotic resistant *Staphylococcus aureus*: a paradigm of adaptive power. Curr Opin Microbiol **2007**; 10:428–35.
39. Oliveira DC, Tomasz A, de Lencastre H. Secrets of success of a human pathogen: molecular evolution of pandemic clones of meticillin-resistant *Staphylococcus aureus*. Lancet Infect Dis **2002**; 2:180–9.
40. Grundmann H, Aanensen DM, van den Wijngaard CC, Spratt BG, Harmsen D, Friedrich AW. Geographic distribution of *Staphylococcus aureus* causing invasive infections in Europe: a molecular-epidemiological analysis. PLoS Med **2010**; 7:e1000215.
41. Burton DC, Edwards JR, Horan TC, Jernigan JA, Fridkin SK. Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997–2007. JAMA **2009**; 301:727–36.
42. Landrum ML, Neumann C, Cook C, et al. Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005–2010. JAMA **2012**; 308:50–9.
43. Centers for Disease Control and Prevention (CDC). Vital signs: central line-associated blood stream infections—United States, 2001, 2008, and 2009. MMWR Morb Mortal Wkly Rep **2011**; 60:243–8.
44. Office for National Statistics. Deaths involving MRSA: England and Wales, 2006 to 2010. 23 August **2011**. Available at: http://www.ons.gov.uk/ons/rel/subnational-health2/deaths-involving-mrsa/2006-to-2010/statistical-bulletin.html. Accessed 13 November 2012.
45. Mohr JF, Murray BE. Point: Vancomycin is not obsolete for the treatment of infection caused by methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis **2007**; 44:1536–42.
46. Tenover FC, Moellering RC Jr. The rationale for revising the Clinical and Laboratory Standards Institute vancomycin minimal inhibitory concentration interpretive criteria for *Staphylococcus aureus*. Clin Infect Dis **2007**; 44:1208–15.
47. Steinkraus G, White R, Friedrich L. Vancomycin MIC creep in non-vancomycin-intermediate *Staphylococcus aureus* (VISA), vancomycin-susceptible clinical methicillin-resistant *S. aureus* (MRSA) blood isolates from 2001–05. J Antimicrob Chemother **2007**; 60:788–94.
48. Wang G, Hindler JF, Ward KW, Bruckner DA. Increased vancomycin MICs for *Staphylococcus aureus* clinical isolates from a university hospital during a 5-year period. J Clin Microbiol **2006**; 44:3883–6.
49. Hiramatsu K, Hanaki H, Ino T, Yabuta K, Oguri T, Tenover FC. Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. J Antimicrob Chemother **1997**; 40:135–6.
50. Hanaki H, Kuwahara-Arai K, Boyle-Vavra S, Daum RS, Labischinski HHiramatsu K. Activated cell-wall synthesis is associated with vancomycin resistance in methicillin-resistant *Staphylococcus aureus* clinical strains Mu3 and Mu50. J Antimicrob Chemother **1998**; 42:199–209.
51. Hanaki H, Labischinski H, Inaba Y, Kondo N, Murakami H, Hiramatsu K. Increase in glutamine-non-amidated muropeptides in the peptidoglycan of vancomycin-resistant *Staphylococcus aureus* strain Mu50. J Antimicrob Chemother **1998**; 42:315–20.
52. Fridkin SK, Hageman J, McDougal LK, et al. Epidemiological and microbiological characterization of infections caused by *Staphylococcus aureus* with reduced susceptibility to vancomycin, United States, 1997–2001. Clin Infect Dis **2003**; 36:429–39.

53. Boyle-Vavra S, Berke SK, Lee JC, Daum RS. Reversion of the glycopeptide resistance phenotype in *Staphylococcus aureus* clinical isolates. Antimicrob Agents Chemother **2000**; 44:272–7.
54. de Lassence A, Hidri N, Timsit JF, et al. Control and outcome of a large outbreak of colonization and infection with glycopeptide-intermediate *Staphylococcus aureus* in an intensive care unit. Clin Infect Dis **2006**; 42:170–8.
55. Saravolatz LD, Pawlak J, Johnson LB. In vitro susceptibilities and molecular analysis of vancomycin-intermediate and vancomycin-resistant *Staphylococcus aureus* isolates. Clin Infect Dis **2012**; 55:582–6.
56. Centers for Disease Control and Prevention (CDC). *Staphylococcus aureus* resistant to vancomycin—United States, 2002. MMWR Morb Mortal Wkly Rep **2002**; 51:565–7.
57. Weigel LM, Clewell DB, Gill SR, et al. Genetic analysis of a high-level vancomycin-resistant isolate of *Staphylococcus aureus*. Science **2003**; 302:1569–71.
58. Network on Antimicrobial Resistance in *S. aureus* (NARSA). Glycopeptide resistant staphylococci. Available at: http://www.narsa.net/control/member/search?repositoryId=99. Accessed 13 November 2012.
59. Hiramatsu K, Aritaka N, Hanaki H, et al. Dissemination in Japanese hospitals of strains of *Staphylococcus aureus* heterogeneously resistant to vancomycin. Lancet **1997**; 350:1670–3.
60. Charles PG, Ward PB, Johnson PD, Howden BP, Grayson ML. Clinical features associated with bacteremia due to heterogeneous vancomycin-intermediate *Staphylococcus aureus*. Clin Infect Dis **2004**; 38:448–51.
61. Tenover FC. The quest to identify heterogeneously resistant vancomycin-intermediate *Staphylococcus aureus* strains. Int J Antimicrob Agents **2010**; 36:303–6.
62. van Hal SJ, Wehrhahn MC, Barbagiannakos T, et al. Performance of various testing methodologies for detection of heteroresistant vancomycin-intermediate *Staphylococcus aureus* in bloodstream isolates. J Clin Microbiol **2011**; 49:1489–94.
63. Richter SS, Satola SW, Crispell EK, et al. Detection of *Staphylococcus aureus* isolates with heterogeneous intermediate-level resistance to vancomycin in the United States. J Clin Microbiol **2011**; 49:4203–7.
64. Rybak MJ, Leonard SN, Rossi KL, Cheung CM, Sader HS, Jones RN. Characterization of vancomycin-heteroresistant *Staphylococcus aureus* from the metropolitan area of Detroit, Michigan, over a 22-year period (1986 to 2007). J Clin Microbiol **2008**; 46:2950–4.
65. Bae IG, Federspiel JJ, Miró JM, et al. Heterogeneous vancomycin-intermediate susceptibility phenotype in bloodstream methicillin-resistant *Staphylococcus aureus* isolates from an international cohort of patients with infective endocarditis: prevalence, genotype, and clinical significance. J Infect Dis **2009**; 200:1355–66.
66. Haque NZ, Zuniga LC, Peyrani P, et al. Relationship of vancomycin minimum inhibitory concentration to mortality in patients with methicillin-resistant *Staphylococcus aureus* hospital-acquired, ventilator-associated, or health-care-associated pneumonia. Chest **2010**; 138:1356–62.
67. Parer S, Lotthe A, Chardon P, Poncet R, Jean-Pierre H, Jumas-Bilak E. An outbreak of heterogeneous glycopeptide-intermediate *Staphylococcus aureus* related to a device source in an intensive care unit. Infect Control Hosp Epidemiol **2012**; 33:167–74.
68. Lowy FD. Antimicrobial resistance: the example of *Staphylococcus aureus*. J Clin Invest **2003**; 111:1265–73.
69. Malachowa N, DeLeo FR. Mobile genetic elements of *Staphylococcus aureus*. Cell Mol Life Sci **2010**; 67:3057–71.
70. Gu B, Kelesidis T, Tsiodras S, Hindler J, Humphries RM. The emerging problem of linezolid-resistant *Staphylococcus*. J Antimicrob Chemother **2013**; 68:4–11.
71. Mishra NN, Yang SJ, Sawa A, et al. Analysis of cell membrane characteristics of in vitro-selected daptomycin-resistant strains of methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **2009**; 53:2312–8.
72. Mehta S, Cuirolo AX, Plata KB, et al. VraSR two-component regulatory system contributes to *mprF*-mediated decreased susceptibility to daptomycin in in vivo-selected clinical strains of methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **2012**; 56: 92–102.
73. Sánchez García M, De la Torre MA, Morales G, et al. Clinical outbreak of linezolid-resistant *Staphylococcus aureus* in an intensive care unit. JAMA **2010**; 303:2260–4.
74. Patel JB, Jevitt LA, Hageman J, McDonald LC, Tenover FC. An association between reduced susceptibility to daptomycin and reduced susceptibility to vancomycin in *Staphylococcus aureus*. Clin Infect Dis **2006**; 42:1652–3.
75. Levine DP, Cushing RD, Jui J, Brown WJ. Community-acquired methicillin-resistant *Staphylococcus aureus* endocarditis in the Detroit Medical Center. Ann Intern Med **1982**; 97:330–8.
76. Udo EE, Pearman JW, Grubb WB. Genetic analysis of community isolates of methicillin-resistant *Staphylococcus aureus* in Western Australia. J Hosp Infect **1993**; 25:97–108.
77. Dufour P, Gillet Y, Bes M, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: emergence of a single clone that produces Panton-Valentine leukocidin. Clin Infect Dis **2002**; 35:819–24.
78. Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*—Minnesota and North Dakota, 1997–1999. MMWR Morb Mortal Wkly Rep **1999**; 48:707–10.
79. Ma XX, Galiana A, Pedreira W, et al. Community-acquired methicillin-resistant *Staphylococcus aureus*, Uruguay. Emerg Infect Dis **2005**; 11:973–6.
80. Wang CC, Lo WT, Chu ML, Siu LK. Epidemiological typing of community-acquired methicillin-resistant *Staphylococcus aureus* isolates from children in Taiwan. Clin Infect Dis **2004**; 39:481–7.
81. Stryjewski ME, Chambers HF. Skin and soft-tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis **2008**; 46 (Suppl 5):S368–77.
82. Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet **2002**; 359:753–9.
83. King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. Ann Intern Med **2006**; 144: 309–17.
84. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med **2006**; 355:666–74.
85. Robert J, Tristan A, Cavalié L, et al. Panton-Valentine leukocidin-positive and toxic shock syndrome toxin 1-positive methicillin-resistant *Staphylococcus aureus*: a French multicenter prospective study in 2008. Antimicrob Agents Chemother **2011**; 55:1734–9.
86. Seybold U, Kourbatova EV, Johnson JG, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infections. Clin Infect Dis **2006**; 42:647–56.
87. Davis SL, Rybak MJ, Amjad M, Kaatz GW, McKinnon PS. Characteristics of patients with healthcare-associated infection due to SCCmec type IV methicillin-resistant *Staphylococcus aureus*. Infect Control Hosp Epidemiol **2006**; 27:1025–31.
88. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant *Staphylococcus aureus* clone USA300 in men who have sex with men. Ann Intern Med **2008**; 148:249–57.
89. Hageman JC, Patel J, Franklin P, et al. Occurrence of a USA300 vancomycin-intermediate *Staphylococcus aureus*. Diagn Microbiol Infect Dis **2008**; 62:440–2.

90. Murthy MH, Olson ME, Wickert RW, Fey PD, Jalali Z. Daptomycin non-susceptible meticillin-resistant *Staphylococcus aureus* USA 300 isolate. J Med Microbiol **2008**; 57:1036–8.
91. Chua K, Laurent F, Coombs G, Grayson ML, Howden BP. Antimicrobial resistance: Not community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA)! A clinician's guide to community MRSA—its evolving antimicrobial resistance and implications for therapy. Clin Infect Dis **2011**; 52:99–114.
92. Deleo FR, Otto M, Kreiswirth BN, Chambers HF. Community-associated meticillin-resistant *Staphylococcus aureus*. Lancet **2010**; 375:1557–68.
93. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AWCarmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* bacteremia: a meta-analysis. Clin Infect Dis **2003**; 36:53–9.
94. Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus* bacteraemia: a meta-analysis. Med J Aust **2001**; 175:264–7.
95. Zahar JR, Clec'h C, Tafflet M, et al. Is methicillin resistance associated with a worse prognosis in *Staphylococcus aureus* ventilator-associated pneumonia? Clin Infect Dis **2005**; 41:1224–31.
96. Combes A, Luyt CE, Fagon JY, et al. Impact of methicillin resistance on outcome of *Staphylococcus aureus* ventilator-associated pneumonia. Am J Respir Crit Care Med **2004**; 170:786–92.
97. Soriano A, Marco F, Martinez JA, et al. Influence of vancomycin minimum inhibitory concentration on the treatment of methicillin-resistant *Staphylococcus aureus* bacteremia. Clin Infect Dis **2008**; 46:193–200.
98. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. Arch Intern Med **2006**; 166:2138–44.
99. Holmes NE, Turnidge JD, Munckhof WJ, et al. Antibiotic choice may not explain poorer outcomes in patients with *Staphylococcus aureus* bacteremia and high vancomycin minimum inhibitory concentrations. J Infect Dis **2011**; 204:340–7.
100. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. Clin Infect Dis **2012**; 54:755–71.
101. van Hal SJ, Paterson DL. Systematic review and meta-analysis of the significance of heterogeneous vancomycin-intermediate *Staphylococcus aureus* isolates. Antimicrob Agents Chemother **2011**; 55:405–10.
102. van Hal SJ, Jones M, Gosbell IB, Paterson DL. Vancomycin heteroresistance is associated with reduced mortality in ST239 methicillin-resistant *Staphylococcus aureus* blood stream infections. PloS One **2011**; 6:e21217.
103. Dunman PM, Murphy E, Haney S, et al. Transcription profiling-based identification of *Staphylococcus aureus* genes regulated by the agr and/or sarA loci. J Bacteriol **2001**; 183:7341–53.
104. Moise PA, Forrest A, Bayer AS, Xiong YQ, Yeaman MR, Sakoulas G. Factors influencing time to vancomycin-induced clearance of nonendocarditis methicillin-resistant *Staphylococcus aureus* bacteremia: role of platelet microbicidal protein killing and agr genotypes. J Infect Dis **2010**; 201:233–40.
105. Fowler VG Jr, Sakoulas G, McIntyre LM, et al. Persistent bacteremia due to methicillin-resistant *Staphylococcus aureus* infection is associated with agr dysfunction and low-level in vitro resistance to thrombin-induced platelet microbicidal protein. J Infect Dis **2004**; 190:1140–9.
106. Moise PA, Sakoulas G, Forrest A, Schentag JJ. Vancomycin in vitro bactericidal activity and its relationship to efficacy in clearance of methicillin-resistant *Staphylococcus aureus* bacteremia. Antimicrob Agents Chemother **2007**; 51:2582–6.
107. Schweizer ML, Furuno JP, Sakoulas G, et al. Increased mortality with accessory gene regulator (agr) dysfunction in *Staphylococcus aureus* among bacteremic patients. Antimicrob Agents Chemother **2011**; 55:1082–7.
108. Lipinska U, Hermans K, Meulemans L, et al. Panton-Valentine leukocidin does play a role in the early stage of *Staphylococcus aureus* skin infections: a rabbit model. PloS One **2011**; 6:e22864.
109. Lina G, Piemont Y, Godail-Gamot F, et al. Involvement of Panton-Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. Clin Infect Dis **1999**; 29:1128–32.
110. Bae IG, Tonthat GT, Stryjewski ME, et al. Presence of genes encoding the panton-valentine leukocidin exotoxin is not the primary determinant of outcome in patients with complicated skin and skin structure infections due to methicillin-resistant *Staphylococcus aureus*: results of a multinational trial. J Clin Microbiol **2009**; 47:3952–7.
111. Lalani T, Federspiel JJ, Boucher HW, et al. Associations between the genotypes of *Staphylococcus aureus* bloodstream isolates and clinical characteristics and outcomes of bacteremic patients. J Clin Microbiol **2008**; 46:2890–6.
112. Peyrani P, Allen M, Wiemken TL, et al. Severity of disease and clinical outcomes in patients with hospital-acquired pneumonia due to methicillin-resistant *Staphylococcus aureus* strains not influenced by the presence of the Panton-Valentine leukocidin gene. Clin Infect Dis **2011**; 53:766–71.
113. Sharma-Kuinkel BK, Ahn SH, Rude TH, et al. Presence of genes encoding Panton-Valentine leukocidin is not the primary determinant of outcome in patients with hospital-acquired pneumonia due to *Staphylococcus aureus*. J Clin Microbiol **2012**; 50:848–56.
114. Skinner D, Keefer CS. Significance of bacteremia caused by *Staphylococcus aureus*. Arch Intern Med **1941**; 68:851–75.
115. de Kraker ME, Wolkewitz M, Davey PG, et al. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant *Staphylococcus aureus* bloodstream infections. Antimicrob Agents Chemother **2011**; 55:1598–605.
116. Kuehnert MJ, Hill HA, Kupronis BA, Tokars JI, Solomon SL, Jernigan DB. Methicillin-resistant–*Staphylococcus aureus* hospitalizations, United States. Emerg Infect Dis **2005**; 11:868–72.
117. Klevens RM, Morrison MA, Nadle J, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. JAMA **2007**; 298:1763–71.
118. Hoyert DL, Xu JQ. Deaths: preliminary data for 2011. Natl Vital Stat Rep **2012**; 61:1–52.