Methicillin-Resistant *Staphylococcus aureus*: An Evolutionary, Epidemiologic, and Therapeutic Odyssey

Stan Deresinski
Division of Infectious Disease and Geographic Medicine, Department of Medicine, Stanford University, Stanford, and Santa Clara Valley Medical Center, San Jose, California

Methicillin-resistant *Staphylococcus aureus*, first identified just over 4 decades ago, has undergone rapid evolutionary changes and epidemiologic expansion. It has spread beyond the confines of health care facilities, emerging anew in the community, where it is rapidly becoming a dominant pathogen. This has led to an important change in the choice of antibiotics in the management of community-acquired infections and has also led to the development of novel antimicrobials.

**HISTORICAL BACKGROUND AND EPIDEMIOLOGY**

It was only 1 year after an Oxfordshire constable, Albert Alexander, became the first recipient of penicillin, that Rammelkamp reported the identification of isolates of *Staphylococcus aureus* resistant to this miracle drug [1]. Infections caused by penicillin-resistant *S. aureus* were initially limited to hospitalized patients and were only later detected in the community, where they eventually became common [2]. In an historical reprise, the identification of methicillin-resistant *S. aureus* (MRSA) was reported within 1 year after the 1960 introduction of this semisynthetic penicillin, and once again, an organism that was initially present only in hospitals later became prevalent in the community [2, 3]. The spread of MRSA from the hospital to the community was a predictable event. The emergence in the past decade of novel strains of MRSA in the community that are genetically distinct from MRSA strains originating in the hospital was perhaps less anticipated.

MRSA is currently the most commonly identified antibiotic-resistant pathogen in US hospitals [4, 5]. Although 25.9% of *S. aureus* strains isolated from outpatients were methicillin resistant [5], most of these strains were recovered from individuals who were likely to have acquired them in the health care environment [6, 7]. Their association with health care may, however, have been indirect; household contacts of individuals with hospital-acquired MRSA (HA-MRSA) are at significantly increased risk for MRSA colonization [8]. In a recent and dramatic evolutionary development, however, infection with novel community-acquired strains of MRSA (CA-MRSA) in previously healthy individuals without either direct or indirect association with health care facilities has emerged as a new and important public health problem [9–11].

In some community settings, CA-MRSA have become the prevalent form of *S. aureus* isolated from cutaneous infections, especially among children. At a Houston pediatric hospital, 74% of community-acquired *S. aureus* strains isolated since 2001 have been resistant to methicillin [12]. Clusters and outbreaks in adolescents and adults have been reported to occur in Native Americans [13], homeless youth [14], men who have sex with men [9], jail inmates [10], military recruits [15], children in child care centers [16], and competitive athletes [17]. Although most infections have involved skin and skin structures, potentially lethal invasive infections have also occurred. The report in 1999 of the deaths of 4 previously healthy children in Minnesota and North Dakota who did not have pre-
vious contact with health care facilities unequivocally illustrated the potential dangers presented by CA-MRSA [18].

Reversing and completing an epidemiologic cycle, CA-MRSA are now being introduced from their site of origin in the community into the hospital [19, 20]. At some hospitals, CA-MRSA are displacing classic hospital-associated strains of S. aureus, which is consistent with the hypothesis that the former may be more fit [21].

**MOLECULAR EPIDEMIOLOGY OF METHICILLIN RESISTANCE**

The mechanism of resistance to methicillin was uncovered in 1981 with the the identification of reduced-affinity penicillin-binding proteins in MRSA [22]. The altered protein, PBP2a (PBP2’ in the United Kingdom), retains effective transpeptidase activity while having reduced affinity for penicillin and other available β-lactam antibiotics. PBP2a exhibit both a reduced rate-constant for acylation by β-lactams and elevated dissociation constants [23]. These 2 factors, acting together, prevent acylation of PBP2a and thus result in β-lactam resistance [23].

PBP2a is encoded by the mecA gene (for a glossary of genetic terms, see Appendix) [24]. The mobile mecA gene complex is comprised of mecA together with its regulator genes, mecI and mecR, and resides within a genomic island, the staphylococcal cassette chromosome mec (SCCmec) that constitutes 1%–2% of the ~2.9 million–bp S. aureus chromosome [24–26] (figure 1). SCCmec also contains the insertion sequence, IS431mec, as well as recombinases necessary for site-specific integration and excision. Some SCCmec types also contain various additional genetic elements, such as Tin554 (which encodes resistance to macrolides, clindamycin, and streptogramin B) and pTI81 (which encodes resistance to tetracyclines) [2].

The expression of PBP2a is induced by the binding of β-lactam antibiotics to a cytoplasmic membrane sensor-transducer receptor encoded by the mecR1 gene, triggering a signal leading to the proteolytic release of the mecI repressor from the operator region of the mecA gene [27, 28]. Phenotypic resistance to methicillin is variably expressed, and population analysis demonstrates that each MRSA strain has a characteristic growth profile at each concentration of methicillin examined [29]. In contrast to this heterogeneously expressed resistance to methicillin, homogeneous resistance requires the interaction of additional factors, such as the femA–F genes that are involved in peptidoglycan synthesis [30].

**MOLECULAR EVOLUTIONARY HISTORY**

Although PFGE is commonly used in hospitals to determine the relatedness of isolates for epidemiologic purposes, this method is insufficiently discriminatory for evolutionary studies [31]. The overall genetic background of S. aureus isolates is unambiguously determined through multilocus sequence typ-

![Figure 1. Diagram showing the staphylococcal cassette chromosome mec type IV (SCCmec type IV) (adapted from [24]). SCCmec type IV lacks antibiotic resistance elements directed at non–β-lactam antibiotics that are present in SCCmec types characteristic of hospital-acquired methicillin-resistant Staphylococcus aureus. ccrA2 and ccrB2 designate cassette chromosome recombinases. Y IS T272 designates IS431mec insertion sequences. mecA encodes PBP2a. orfX indicates an open reading frame. ΔmecR1 is a signal transducer gene whose activation by β-lactam antibiotics inactivates the mecI repressor gene product, allowing expression of mecA.](https://academic.oup.com/cid/article-abstract/40/4/562/353410)
SCC-MRSA, is a strain originating in Denmark and possessing MRSA and CA-MRSA clones [31, 35, 41, 42].

Already successfully adapted to hospital environments and to the community have, in turn, created successful epidemic HA-MRSA and CA-MRSA clones [31, 35, 41, 42].

Evidence indicates that the ancestral MRSA genotype, ST250-MRSA, is a strain originating in Denmark and possessing SCCmec type I, most extant isolates of which were obtained in the 1960s [37]. (By convention, strains are named by their sequence type [ST] and the presence or absence of methicillin resistance. Thus, this strain is a methicillin-resistant S. aureus of a sequence type designated as 250). ST250-MRSA arose as the consequence of the acquisition of the mec gene by the methicillin-susceptible strain ST250-MSSA, which had itself arisen from ST8-MSSA by a chromosomal point mutation [37]. ST250-MRSA is no longer a major cause of epidemic MRSA infections, but ST247-MRSA (the “Iberian clone”), which evolved from ST250-MRSA by a single point mutation, remains an important hospital pathogen in Europe and has been reported to have caused an outbreak in a New York City hospital [43]. As indicated above, there have since been multiple introductions of mec into S. aureus [31]. The emergence of CA-MRSA strains, in particular, has repeatedly occurred as a result of the introduction of SCCmec type IV into a variety of genetic MSSA backgrounds [41]. In the United States, one of the resultant clones, ST8-MSSA (USA 300) has proven increasingly successful [44].

### EPIDEMIOLOGIC SUCCESS AND VIRULENCE OF CA-MRSA

CA-MRSA strains differ in a number of important ways from the 6 major pandemic clones of MRSA that account for nearly 70% of epidemic HA-MRSA strains [45]. These differences are found in the composition of the gene cassette coding for methicillin resistance, in the carriage of plasmids encoding resistance to antibiotics of other classes (as well as resistance to heavy metals), and in their associated virulence factors.

The earliest strain of MRSA in which SCCmec type IV has been identified was isolated in 1981 [32]. Despite this apparently recent emergence, an analysis of a large number of MRSA isolates detected SCCmec type IV in twice as many clones as any of the other types, suggesting its greater promiscuity and successful persistence [26]. This may be the result of greater efficiency of transfer and/or a lesser fitness cost to the recipient clone, possibly because of its smaller size and lack of the “excess baggage” included in other SCCmec types [26, 35, 41]. Although HA-MRSA has been reported to replicate more slowly than MSSA [46], a CA-MRSA clinical isolate harboring SCCmec type IV has been demonstrated to replicate more rapidly than HA-MRSA isolates with other SCCmec types [41, 42]. In contrast, transformation of an SCCmec type I element into S. aureus strains yielded highly oxacillin-resistant transformants with a reduced growth rate [47]. This relatively greater fitness of CA-MRSA strains carrying SCCmec type IV may account for its remarkable success in displacing other MRSA strains in some hospitals after its introduction from the community [21].

### TABLE 1. Characteristics of staphylococcal cassette chromosome mec (SCCmec) types I–V.

<table>
<thead>
<tr>
<th>SCCmec type</th>
<th>SCCmec size, kb</th>
<th>Other antibiotic-resistant elements (gene) on SCCmec</th>
<th>Origin of S. aureus isolates carrying the specified SCCmec type</th>
<th>Presence of Panton-Valentine leukocidin in S. aureus isolates carrying the specified SCCmec type</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>34</td>
<td>…</td>
<td>Hospital</td>
<td>Infrequent</td>
</tr>
<tr>
<td>II</td>
<td>53</td>
<td>PUB110 (aadD)&lt;sup&gt;5&lt;/sup&gt;, Tn554 (ermA)&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Hospital</td>
<td>Infrequent</td>
</tr>
<tr>
<td>III</td>
<td>67</td>
<td>PUB110 (aadD)&lt;sup&gt;5&lt;/sup&gt;, PT181 (tetK)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>Hospital</td>
<td>Infrequent</td>
</tr>
<tr>
<td>IV</td>
<td>21–24</td>
<td>…</td>
<td>Community</td>
<td>Frequent</td>
</tr>
<tr>
<td>V</td>
<td>28</td>
<td>…</td>
<td>Community</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**NOTE.** Data is adapted from [40] and [155]. PVL, Panton-Valentine leukocidin; S. aureus, Staphylococcus aureus.

- In general, <5% of S. aureus strains that carry SCCmec types I–III also carry the PVL gene; with some exceptions, 40%–90% of S. aureus strains that carry SCCmec type IV carry the PVL gene.
- Encodes resistance to tobramycin and kanamycin.
- Encodes resistance to macrolide-lincosamide-streptogramin antibiotics.
- Encodes resistance to tetracycline.

Sequencing of the genome of CA-MRSA strain MW2, which caused fatal sepsis in a 16-month-old girl from North Dakota [18], identified 19 putative virulence genes not found in 5 simultaneously examined HA-MRSA strains [42]. These included genes for several superantigens, such as enterotoxins B and C, as well as the amphipathic leukotoxin, the Panton-Valentine leukocidin (PVL). PVL, first described in 1932 [48], is a bicomponent synergohymenotropic (synergistic membrane-tropic) toxin that was present in <5% of unselected S.
**aureus** isolates but is present in the majority of CA-MRSA isolates studied [49, 50]. CA-MRSA isolates from Australia, on the other hand, infrequently carry the genes encoding PVL [36].

PVL is encoded by contiguously located cotranscribed genes, lukS-PV and lukF-PV, inserted near the att site [50]. These genes are transmitted by a temperate phage designated oPVL [51, 52]. Their gene products, 33 kDa and 34 kDa in size, respectively, assemble as hetero-oligomers and synergistically exert cytolytic pore-forming activity specifically directed at the cell membranes of polymorphonuclear neutrophils and monocytes and/or macrophages [49, 50]. Injection of PVL into the skin of rabbits causes dermal necrosis [53], suggesting that it may play a role in the severity of skin and skin-structure infections in humans. In addition, an association between PVL-containing strains of MRSA and virulent necrotizing pneumonia has been reported [54].

**RESISTANCE TO ANTIBIOTICS OTHER THAN β-LACTAMS**

In contrast to the multidrug resistance usually seen in HA-MRSA strains, antibiotic resistance in CA-MRSA strains is often limited to β-lactams. The small size of SCCmec type IV may preclude its carriage of additional genetic material, in contrast to the characteristic presence of additional genetic material in SCCmec type II and SCCmec type III [25, 26]. This does not, however, preclude chromosomally encoded resistance or the presence of resistance plasmids in strains carrying any of the mec types. For instance, some CA-MRSA strains isolated in western Australia contain a 41.4-kb plasmid encoding resistance to tetracycline and trimethoprim, as well as resistance to mupirocin and cadmium [55, 56]. Fluoroquinolone resistance is frequent in CA-MRSA carrying SCCmec type IV isolated from homeless youth in San Francisco [57]. Nonetheless, in contrast to HA-MRSA strains, most CA-MRSA isolates remain susceptible to tetracyclines, clindamycin, and trimethoprim-sulfamethoxazole (TMP-SMZ) [11].

**AVAILABLE ANTIBIOTICS FOR THE TREATMENT OF MRSA INFECTION**

**Vancomycin.** Compared with β-lactam therapy, vancomycin therapy has been associated with slower clinical response and longer duration of MSSA bacteremia, and it has been associated with more frequent complications in patients with endocarditis [58, 59]. Failure of vancomycin therapy may be observed in the treatment of patients with bacteremia due to strains of MRSA that have MICs of vancomycin well within the range considered susceptible [60]. Heterogeneous vancomycin resistance, which is not readily detected by routine clinical laboratory methodology, is also associated with failure of vancomycin therapy [61, 62]. The appearance of vancomycin-intermediate **aureus** and, more recently, vancomycin-resistant **aureus** is of further concern [63].

**Quinupristin/dalfopristin.** This combination is active in vitro against MSSA and MRSA [64]. It is bactericidal against **aureus**, although in the presence of constitutive expression of macrolide-lincosamide-streptogramin resistance, it is only bacteriostatic [65]. In a randomized trial, patients with nosocomial MRSA pneumonia who received quinupristin/dalfopristin had a clinical response rate of 19.4%, compared with 40% in vancomycin recipients [66].

**Linezolid.** Linezolid and vancomycin yielded comparable results in hospitalized patients with MRSA infections at a variety of anatomic sites in a randomized, open-label trial [67], as well as in the treatment of skin and skin-structure infections caused by gram-positive organisms [68]. A retrospective subset analysis of 2 prospective randomized clinical trials found evidence suggesting that linezolid was superior to vancomycin in the treatment of hospital-acquired pneumonia due to MRSA [69, 70].

**Daptomycin.** Daptomycin is a novel lipopeptide antibiotic with bactericidal activity against **aureus** that binds, in a calcium-dependent manner, to the bacterial cell membrane, disrupting membrane potential [71]. Daptomycin has received approval from the US Food and Drug Administration for the treatment of complicated skin and skin-structure infections due to susceptible gram-positive pathogens [72]. Daptomycin therapy failed in a trial involving patients with community-acquired pneumonia; daptomycin not only has limited penetration into pulmonary epithelial lining fluid, but its activity is inhibited by pulmonary surfactant [72, 73].

**Tetracyclines.** In vitro susceptibility results involving tetracycline derivatives must be interpreted with caution, because **aureus** isolates that are tetracycline-resistant but that have relatively low MICs of doxycycline and/or minocycline may, in fact, harbor inducible efflux genes [74, 75]. Minocycline has been shown to have bactericidal activity similar to that of vancomycin against a single strain of MRSA in an animal model of endocarditis [76]. Of 14 patients with MRSA infection who were treated with doxycycline or minocycline, either alone or in combination with rifampin, 3 (21%) experienced treatment failure [77].

**TMP-SMZ.** TMP-SMZ was less active than vancomycin in a rabbit model of MRSA endocarditis and less rapidly bactericidal than nafcillin in a rabbit model of MSSA meningitis [78, 79]. A randomized trial of treatment of **aureus** infections, 47% of which were due to MRSA, concluded that treatment with TMP-SMZ was inferior to treatment with vancomycin [80]. An extensive literature review, however, concluded that TMP-SMZ "may be effective for the treatment of infections due to low bacterial burdens of susceptible strains of **aureus**" [81, pg. 340].

**Fluoroquinolones.** Although most CA-MRSA strains are
reported to be fluoroquinolone susceptible, this is not true in some locales [36, 57]. Fluoroquinolone resistance emerged very rapidly in HA-MRSA in the years after widespread utilization of agents of this class; at one institution, fluoroquinolone resistance increased from 7% before 1988 to 83% in 1990 [82]. In vitro passage of both fluoroquinolone-susceptible MSSA and MRSA in the presence of either ciprofloxacin or levofloxacin is associated with the frequent selection of clones resistant to these antibiotics [83]. Furthermore, fluoroquinolones select MRSA from among heterogeneously methicillin-resistant populations in vitro [84], and fluoroquinolone use is associated with an increased risk of nosocomial acquisition of MRSA (but not of MSSA) [85]. The fluoroquinolones with C8 substitutions, such as gatifloxacin and moxifloxacin, appear to be more potent against S. aureus than are older drugs of this class, and they may be less likely to select resistant mutants, an effect that may be strengthened by the addition of rifampin [86–88].

**Clindamycin.** Clindamycin has been used successfully in the treatment of invasive CA-MRSA infections in children [89, 90]. Inducible resistance to clindamycin, however, is not detected by routine susceptibility testing, but requires the use of other methods (e.g., a double-disk diffusion test) [90–93]. Flattening of the zone in the area between the disks to resemble the letter "D" indicates the presence of inducible resistance (figure 2 and table 2).

**Rifampin.** Rifampin selects resistant mutants from among both MSSA and MRSA strains at a frequency of $10^{-7}$ to $10^{-8}$, but this may be prevented by using rifampin in combination with a second active drug [94].

**Topical agents.** MRSA strains that are resistant to mupirocin, mutants of which can be selected in vitro at frequencies of $10^{-7}$ to $10^{-8}$, are reported with increasing frequency [95]. MRSA isolates with elevated MICs of triclosan have been identified [96, 97].

**OVERVIEW OF CHOICE OF SYSTEMIC ANTIBIOTIC THERAPY**

For some infections that require parenteral therapy and are due to MRSA strains that are multidrug resistant, the treatment choices may be restricted to vancomycin, daptomycin, linezolid, and quinupristin/dalfopristin therapy. The potential superiority of linezolid therapy over vancomycin therapy in treating nosocomial pneumonia due to MRSA has been noted [69, 70]. Daptomycin is ineffective in the treatment of pneumonia (Cubist Pharmaceuticals, data on file). The bacteriostatic activity of linezolid may prove to limit its effectiveness in circumstances in which bactericidal activity is required [67].

Choices for treatment of infections due to CA-MRSA may include, in addition to the drugs mentioned above, TMP-SMZ, tetracyclines, clindamycin, and fluoroquinolones. The widespread use of fluoroquinolones for treating these infections may, if history repeats itself, lead to the rapid emergence of resistance to this class of antibiotics. Tetracycline therapy, contraindicated in children and in those who are pregnant, may prove to be effective, but further clinical data are required. TMP-SMZ appears to be effective in treating infections of limited extent and severity. Linezolid is an effective agent for which
use has been limited by its cost. Antibiotic therapy is not always required: a retrospective analysis has found resolution of CA-MRSA infection in children with subcutaneous abscesses ≤5 cm in diameter who underwent incision and drainage in the absence of administration of an antibiotic to which the pathogen was susceptible [98].

INVESTIGATIONAL AGENTS WITH ACTIVITY AGAINST MRSA

Semisynthetic glycopeptides. Oritavancin is a semisynthetic glycopeptide derivative that is active against some vancomycin-resistant, gram-positive bacteria [99, 100]. A randomized trial of oritavancin in the treatment of skin and skin-structure infections demonstrated results comparable to those observed with a vancomycin-based regimen [101]. Its mean terminal plasma half-life (± SD) of 151 ± 39 h allowed it to be given in a total of 3 daily doses [101, 102].

Dalbavancin has a terminal plasma half-life of 9–12 days [103]. A total of 2 doses given 1 week apart in the treatment of skin and skin-structure infections resulted in a 94% cure rate, compared with a 76.2% cure rate in those patients randomized to receive standard-of-care [103]. A third drug of this class, telavancin, with a terminal plasma half-life of 7 h in young volunteers and 11 h in elderly subjects, was effective in a neutropenic mouse thigh model and is also in clinical trials [104–107].

Glycylcyclines. The minocycline derivative tigecycline has bacteriostatic activity against both MSSA and MSRA, including tetracycline-resistant strains [99, 108, 109]. In a randomized dose-comparison study, clinical cure rates were 67% and 74% in patients with skin and skin-structure infections who received 25 mg and 50 mg daily, respectively [110].

Novel β-lactams. A series of β-lactamase–stable cephalosporins with high affinity for PBP2a are in clinical development [111]. The PBP2a affinity of BMS-247243 is 100-fold greater than that of methicillin or cefotaxime, and the drug is bactericidal against MRSA at twice the rate of vancomycin [112]. Other drugs of this class in development include the zwitterionic cephem RWJ-54428 [113], CB-181963 [114], BAL5788 [115], a prodrug of BAL9141 [116, 117], and S-3578 [118]. ME1036 (formerly CP5609) is a C2-modified carbapenem with high affinity for PBP2a and with an MIC90 of 2.0 μg/mL against MRSA [119]. SM-197436, SM-232721, and SM-232724 are novel methylcarbapenems that are also active in vitro against MRSA [120].

Fluoroquinolones. DW286, a naphthyridone, is among several fluoroquinolones in development that have in vitro activity against MRSA [121]. Active against MRSA strains that are resistant to other fluoroquinolones, it selects fluoroquinolone-resistant mutants at a lower frequency than do older agents (as may another fluoroquinolone, ABT-492) [122, 123].

Oligosaccharides. Evernimicin is a complex sugar derivative with a novel mode of action [124, 125]. A related compound, avilamycin, has been used in animal feed, raising the specter of rapid emergence of resistance to this class of drugs [126].

Miscellaneous antimicrobials. The rifamycin rifabutin retains activity against some isolates that are resistant to rifampin [127]. Epirepristin is a dihydrofolate reductase inhibitor with activity against some trimethoprim-resistant strains of S. aureus; its combination with dapson results in in vitro activity against S. aureus that is greater than that of TMP-SMZ [128]. Iclaprim is another dihydrofolate reductase inhibitor with activity against MRSA [129].

Other examples of modifications of existing molecules with antistaphylococcal activity include the oxazolidinones ranbenzolid [130, 131] and eperezolid [129, 132], as well as N-acetylated ornithine analogues of daptomycin [133]. Among drugs with novel targets are the peptide deformylase–inhibitors NVP-PDF 713 [134, 135] and BB-83698 [136].

A number of naturally occurring cationic proteins have in vitro activity against S. aureus [137], and some have been demonstrated to have activity in animal models of infection [138]. Lysozyme is active in vitro against S. aureus [139] and was effective in a rabbit model of MRSA endocarditis [140]. Its use in a patient with S. aureus infection and neutropenia was first reported in 1974 [141]. Specific bacteriophage has been demonstrated to be effective in protecting mice against lethal S. aureus infection [142, 143].

Targeting virulence factors. RNAIII-inhibiting peptide inhibits S. aureus pathogenesis by disrupting quorum-sensing mechanisms [144]. The accessory gene regulator (agr) is an important regulator of virulence that is, at least in part, related to quorum sensing [145]; a truncated thiolactone peptide has been found to be a potent inhibitor for all 4 agr-specificity groups of S. aureus [146].

S. aureus immune globulin intravenous (human) (Altastaph; NABI Biopharmaceuticals) is a hyperimmune, polyclonal, intravenous immunoglobulin product derived from the plasma of human donors who have previously been vaccinated with S. aureus polysaccharide conjugate vaccine (StaphVAX; NABI Biopharmaceuticals), a bivalent conjugate capsular polysaccharide covalently bound to recombinant exoprotein A, which has been demonstrated to provide temporary protection against the occurrence of S. aureus bacteremia in patients receiving hemodialysis [147, 148]. Patients with S. aureus bacteremia and persisting fever are currently being enrolled in a phase I/II trial [149]. Also in progress is a phase II prevention trial involving infants with low birth weights [150].

Tefibazumab (Aurexix; Inhibetix) is a humanized monoclonal antibody directed at the microbial surface components recognizing adhesive matrix molecule (MSCRAMM) clumping
factor A [151] that is currently being evaluated in a phase II trial in patients with *S. aureus* bacteremia [152]. INH-A21 (Vepronate; Inhibitex) is a donor-selected human polyclonal immunoglobulin preparation that is also enriched in antibody to staphylococcal MSCRAMM proteins and that is undergoing clinical trial evaluation for the prevention of infection in infants with very low birth weights [153]. Another cell surface component, teichoic acid, is the target of BYSX-A110, an IgG1 chimeric monoclonal antibody that is in clinical trials for the prevention of staphylococcal infections in infants with low birth weights [154].

Aurograb (NeuTec Pharma) is a single-chain antibody fragment lacking the immunoglobulin Fc domain targeted at EMRSA-15, a 61-kDa ABC transporter expressed by epidemic strains of MRSA that is in clinical therapeutic trials in the United Kingdom [155, 156].

Pooled intravenous immune globulin preparations neutralize a number of staphylococcal superantigen toxins and, as a consequence, are commonly used in the therapy of toxic shock syndrome [157]. The identification of a conserved epitope on staphylococcal enterotoxins that appears to be critical to their activity raises the possibility of another approach to superantigen neutralization [158]. PVL can also be neutralized in vitro by commercial intravenous immunoglobulin preparations [159].

The story of antibiotic resistance and virulence in *S. aureus* is, as has been stated by others, one of “depressing evolutionary progression” [37, pg. 92]. The emergence of CA-MRSA, the rapid introduction of SCC*mec* type IV into multiple genetic backgrounds, and the epidemiological success of the resultant strains indicate that this problem will continue its inexorable march [37, 160, 161]. Mathematical modeling demonstrates difficulty in the epidemiologic control of MRSA in the face of its increased prevalence in the community and the increasingly daunting tasks for hospital infection-control programs [162]. An effective vaccine will be the only effective long-term solution.

### Acknowledgments

Potential conflicts of interest. S.D. is a member of the speakers bureau of Pfizer and is a consultant for Therapeutic Human Monoclonals.

### APPENDIX

**Cassette chromosome recombinase (ccr)**  A gene necessary for the mobility of SCC that enables its site-specific integration into and precise excision from the *S. aureus* chromosome.

**Genomic island**  Genomic islands (often abbreviated as GIS or GEIs) are horizontally acquired chromosomal regions of DNA carrying several genes encoding traits associated with increased adaptability or fitness under specific conditions. They are termed pathogenicity, fitness, symbiosis, metabolic, or resistance islands, depending on the functions encoded [163].

**Housekeeping gene**  A gene involved in basic functions required for cell viability and constitutively expressed in most cells. Housekeeping genes evolve much more slowly than do tissue specific genes that encode proteins necessary only in selected types of cells.

**Insertion sequence**  A DNA sequence involved in the mobilization of genetic information to and from vectors such as plasmids.

**mec gene complex**  Gene complex composed of *mecA* and its regulator genes, *mecI* and *mecR*.

*mecA*  The gene encoding PBP2a, responsible for resistance to methicillin and other β-lactam antibiotics.

*mecI*  The *mecA* repressor gene.

*mecR1*  A signal transducer gene that encodes a transmembrane receptor that responds to covalent binding of a β-lactam antibiotic and its extracellular sensor domain. Binding initiates events that lead to inactivation of the *mecI* gene repressor product by a protease, allowing expression of *mecA*.

**Staphylococcal chromosome cassette (SCC)**  SCC (or SCC*mec*) is a mobile, 52-kb DNA cassette containing the gene that encodes resistance to methicillin (*mecA*), as well as those

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### Table 2. Macrolide-lincosamide-streptogramin resistance in methicillin-resistant *Staphylococcus aureus*.

<table>
<thead>
<tr>
<th>Mechanism of resistance</th>
<th>Gene determinant</th>
<th>Erythromycin</th>
<th>Clindamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efflux</td>
<td><em>msrA</em></td>
<td>Resistant</td>
<td>Susceptible</td>
</tr>
<tr>
<td>Ribosomal methylation</td>
<td><em>erm</em></td>
<td>Resistant</td>
<td>Susceptible or resistant (inducible),(^a) resistant (constitutive)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are adapted from [34].

\(^a\) Resistant strains have inducible resistance. Determination of resistance requires specific testing (e.g., use of a double-disk diffusion test).
genes (ccrA and ccrB in most cases) that encode the integration and excision necessary for its recombinase in the staphylococcal chromosome, in addition to insertion sequences.

References


74. Tracinski K, Cooper BS, Hyniewicz W, Dowson CG. Expression of

75. Schmitz FJ, Krey A, Sadurski R, et al. Resistance to tetracycline and distribution of tetracycline resistance genes in European *Staphylo-


77. Ruhe JJ, Monson TP. Use of tetracyclines for infections caused by methicillin-resistant *Staphylococcus aureus* [abstract 516]. In: Program and abstracts of the 42nd Annual Meeting Meeting of the Infectious Disease Society of America, 30 September–3 October, 2004, Boston, Massachusetts.

78. de Gorgolas M, Aviles P, Verdejo C, Fernandez Guerrero ML. Treatment of experimental endocarditis due to methicillin-susceptible or methicillin-resistant *Staphylococcus aureus* with trimethoprim-sulfa-methoxazole and antibiotics that inhibit cell wall synthesis. Antimi-

79. Scheld WM, Keeley JM, Field MR, Broder J. Co-trimoxazole versus nafcillin in the therapy of experimental meningitis due to *Staphy-

80. Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphy-


82. Hershoc RW, Khayr WF, Schreckenberger PC. Ciprofloxacin resis-

83. Limoncu MH, Ermentcan S, Cetin CB, et al. Emergence of phenotypic resistance to ciprofloxacin and levofloxacin in methicillin-resistant and methicillin-sensitive *Staphylococcus aureus* strains. Int J Antimi-

84. Venezia RA, Domaracki BE, Evans AM, et al. Selection of high-level oxacillin resistance in heteroresistant *Staphylococcus aureus* by fluoro-

85. Weber SG, Gold HS, Hooper DC, et al. Fluoroquinolones and the risk for methicillin-resistant *Staphylococcus aureus* in hospitalized pa-


89. Martinez-Aguilar G, Hammerman WA, Mason EO Jr, Kaplan SL. Clindamycin treatment of invasive infections caused by community-


91. Siberry GK, Tekele T, Carroll K, Dick J. Failure of clindamycin treat-
ment of methicillin-resistant *Staphylococcus aureus* expressing induc-


93. Centers for Disease Control and Prevention. Testing/reporting pro-


97. Fan F, Yan K, Wallis NG, et al. Defining and combating the mech-


102. Fetterly GJ, Ong C, Bhavnani SM, et al. Characterization of orita-


104. King A, Phillips I, Kaniga K. Comparative in vitro activity of telavancin (TD-6424), a rapidly bactericidal, concentration-dependent anti-in-
fective with multiple mechanisms of action against gram-positive bac-

105. Clinical trial: telavancin (TD-6424, arbelic) for treatment of uncom-


110. Postier RG, Green SL, Klein SR, et al. Results of a multicenter, ran-


116. Entenza JM, Hohl P, Heinze-Krauss I, et al. BAL9141, a novel ex-


