REVIEW ARTICLE

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

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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-

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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 consisitent 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* (SCC*mec*) that constitutes 1%–2% of the ~2.9 million–bp *S. aureus* chromosome [24–26] (figure 1). SCC*mec* also contains the insertion sequence, IS431*mec,* as well as recombinases necessary for site-specific integration and excision. Some SCC*mec* types also contain various additional genetic elements, such as *Tn554* (which encodes resistance to macrolides, clindamycin, and streptogramin B) and *pT18*1 (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 typing by determination of the sequence of portions of 7 housekeeping genes [25]. The mobile SCC*mec* elements, on the other hand, are classified by analysis of their cassette chromosome recombinase (*ccr*) and *mecA* gene complexes [32]. SCC*mec* types also differ with regard to their acquisition of resistance determinants acquired as the result of integration of plasmids and transposons [32]. At least 5 SCC*mec* types (types I–V), varying in size from ~20 kb to 68 kb, have been identified [33] (table 1). The smallest of these—SCC*mec* types I, IV, and V—contain only recombinase genes and the structural and regulatory genes for resistance to methicillin and lack the transposable elements and genes encoding resistance to non–β-lactam antibiotics carried by types II and III [33, 35]. SCC*mec* types I-IV contain alleles of *ccrA* and *ccrB,* whereas type V, which has to date been identified in a small number of Australian CA-MRSA isolates, contains a novel *ccr* designated *ccrC* [33]. Two possible additional SCC*mec* types have recently been identified among Australian CA-MRSA strains [36].

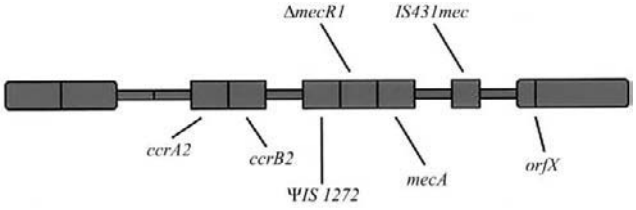

Figure 1. Diagram showing the staphylococcal cassette chromosome *mec* type IV (SCC*mec* type IV) (adapted from [24]). SCC*mec* type IV lacks antibiotic resistance elements directed at non–β-lactam antibiotics that are present in SCC*mec* types characteristic of hospital-acquired methicillin-resistant *Staphylococcus aureus. ccrA2* and *ccrB2* designate cassette chromosome recombinases. ΨIS *1272* designates IS*431mec* insertion sequences. *mecA* encodes PBP2a. *orfX* indicates an open reading frame. Δ*mecR1* is a signal transducer gene whose activation by β-lactam antibiotics inactivates the *mecI* repressor gene product, allowing expression of *mecA.*

Genetic evolutionary analyses have demonstrated that the *mecA* gene has been transferred into methicillin-susceptible *S. aureus* (MSSA) on ⩾20 occasions, having emerged in ⩾5 phylogenetically distinct lineages (as well as reemerging within individual lineages) [25, 31, 37]. It has been suggested that the emergence of PBP2a initially resulted from a recombination event involving the genes encoding an existing PBP and an inducible β-lactamase [38]. The donor strains that became the source of PBP2a are likely to have been coagulase-negative staphylococci, with *Staphylococcus sciuri* identified as a prime candidate [39]. A recent study of 44 methicillin-resistant *Staphylococcus epidermidis* isolates from the blood of patients with prosthetic valve endocarditis from 1973 to 1983 found that 2% carried SCC*mec* type I, 34% carried type II, 28% carried type III, and 36% carried type IV [40]. The introduction of *mecA* from the putative donor species into MSSA strains that are

Table 1. Characteristics of staphylococcal cassette chromosome *mec* (SCC*mec*) types I–V.

SCC*mec* type	SCC*mec* size, kb	Other antibiotic-resistant elements (gene) on SCC*mec*	Origin of *S. aureus* isolatates carrying the specified SCC*mec* type	Presence of Panton-Valentine leukocidin in *S. aureus* isolates carrying the specified SCC*mec* type[a]
I	34	…	Hospital	Infrequent
II	53	PUB110 *(aadD)*[b], Tn554 *(ermA)*[c]	Hospital	Infrequent
III	67	PUB110 *(aadD)*[b], PT181 *(tetK)*[d]	Hospital	Infrequent
IV	21–24	…	Community	Frequent
V	28	…	Community	Unknown

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

[a] In general, <5% of *S. aureus* strains that carry SCC*mec* types I–III also carry the PVL gene; with some exceptions, 40%–90% of *S. aureus* strains that carry SCC*mec* type IV carry the PVL gene.

[b] Encodes resistance to tobramycin and kanamycin.

[c] Encodes resistance to macrolide-lincosamide-streptogramin antibiotics.

[d] Encodes resistance to tetracycline.

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 SCC*mec* 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 SCC*mec* 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 SCC*mec* 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 SCC*mec* 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 SCC*mec* types [26, 35, 41]. Although HA-MRSA has been reported to replicate more slowly than MSSA [46], a CA-MRSA clinical isolate harboring SCC*mec* type IV has been demonstrated to replicate more rapidly than HA-MRSA isolates with other SCC*mec* types [41, 42]. In contrast, transformation of an SCC*mec* 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 SCC*mec* type IV may account for its remarkable success in displacing other MRSA strains in some hospitals after its introduction from the community [21].

MOLECULAR BASIS OF VIRULENCE OF CA-MRSA

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 øPVL [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 polymorphonucelar 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 SCC*mec* type IV may preclude its carriage of additional genetic material, in contrast to the characteristic presence of additional genetic material in SCC*mec* type II and SCC*mec* 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 SCC*mec* 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 *S. aureus* and, more recently, vancomycin-resistant *S. aureus* is of further concern [63].

Quinupristin/dalfopristin. This combination is active in vitro against MSSA and MRSA [64]. It is bactericidal against *S. 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 *S. 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 *S. 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 *S. 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 *S. 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^{-6} 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

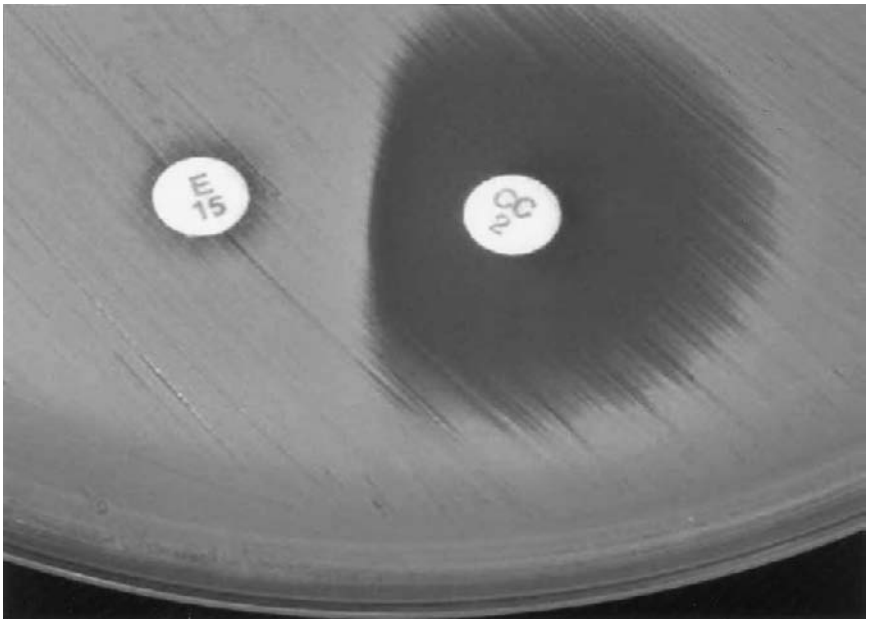

Figure 2. Image shows the results of a double-disk diffusion test for inducible, *erm*-mediated resistance to clindamycin. The demonstration of flattening of the clindamycin zone between the disks is indicative of inducible resistance to clindamycin [34].

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 ($\pm$SD) of 151 $\pm$ 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 MIC_{90} 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 rifalazil retains activity against some isolates that are resistant to rifampin [127]. Epiroprim is a dihydrofolate reductase inhibitor with activity against some trimethoprim-resistant strains of *S. aureus*; its combination with dapsone 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 ranbezolid [130, 131] and eperezolid [129, 132], as well as N-acylated 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]. Lysostaphin 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 (Aurexis; Inhibitex) is a humanized monoclonal antibody directed at the microbial surface components recognizing adhesive matrix molecule (MSCRAMM) clumping

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

Mechanism of resistance	Gene determinant	Drug resistance	
		Erythromycin	Clindamycin
Efflux	*msrA*	Resistant	Susceptible
Ribosomal methylation	*erm*	Resistant	Susceptible or resistant (inducible);[a] resistant (constitutive)

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).

factor A [151] that is currently being evaluated in a phase II trial in patients with *S. aureus* bacteremia [152]. INH-A21 (Veronate; 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.

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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

genes (*ccrA* and *ccrB* in most cases) that encode the integration and excision necessary for its recombination in the staphylococcal chromosome, in addition to insertion sequences.

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