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REVIEW

Improved understanding of factors driving methicillin-resistant *Staphylococcus aureus* epidemic waves

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Abstract: Methicillin-resistant *Staphylococcus aureus* (MRSA) remains one of the most important causes of nosocomial infections worldwide. Since the global spread of MRSA in the 1960s, MRSA strains have evolved with increased pathogenic potential. Notably, some strains are now capable of causing persistent infections not only in hospitalized patients but also in healthy individuals in the community. Furthermore, MRSA is increasingly associated with infections among livestock-associated workers, primarily because of transmission from animals to humans. Moreover, many MRSA strains have gained resistance to most available antibiotics. In this review, we will present current knowledge on MRSA epidemiology and discuss new endeavors being undertaken to understand better the molecular and epidemiological underpinnings of MRSA outbreaks.

Keywords: Staphylococcus aureus, MRSA, nosocomial infection, community-associated infection

Introduction

Infection caused by bacterial pathogens is a global problem. In many cases, bacterial resistance to antimicrobial agents may considerably complicate treatment.[1] Several infectious strains have acquired resistance toward most available antibiotics, which warrants global surveillance and antimicrobial stewardship in addition to increased research efforts to understand the mechanisms underlying pathogenesis and antimicrobial resistance. This is especially true in the case of methicillin-resistant *Staphylococcus aureus* (MRSA) which is one of the most prominent pathogens associated with hospital-, community-, and livestock-associated infections.[2] In this review, we discuss the epidemiology, pathophysiology, and impact on clinical practice of MRSA infections. In addition to this, we highlight important recent research efforts aimed at bettering understanding the key factors that drive MRSA epidemics.

History of MRSA

S. aureus has been associated with human infections since prehistoric times.[3] Due to its prominence as a health-care-related pathogen, it has been a cause of serious concern for clinicians for over a century.[4] Following the introduction of penicillin in the 1940s, the first antimicrobial drug of its kind showing high effectiveness against staphylococcal infections, *S. aureus* developed penicillin resistance within a few months.[5,6] The molecular determinant responsible for penicillin resistance was shown to be a plasmid-encoded β-lactamase gene capable of cleaving the β-lactam ring of penicillin.[7,8] Within about two decades, penicillin resistance in *S. aureus* became a global problem.[9]

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Methicillin, a semisynthetic derivative of penicillin that is resistant to cleavage by β-lactamase, was introduced into clinical use in 1959. Soon afterwards, infections caused by penicillin-resistant strains sharply declined.[10] However, within just 2 years following the introduction of methicillin, the first MRSA strains were isolated in hospitals in the UK.[11] Thereafter, MRSA became endemic worldwide.[4] The molecular determinant of methicillin resistance in MRSA was later shown to be a mobile genetic element (MGE), staphylococcal chromosome cassette mec (SCC*mec*),[12] which harbors the *mecA* gene encoding a penicillin-binding protein (PBP2a/PBP2′) with reduced affinity towards methicillin.[13,14] As a result, methicillin cannot bind to the bacterial cell efficiently, leading to reduced capacity to inhibit bacterial cell-wall synthesis.

Of note, the term MRSA is used loosely, since methicillin sensu stricto is no longer applied in health-care settings. According to the Centers for Disease Control and Prevention, the definition of MRSA spans resistance of *S. aureus* not only against methicillin but also other related, more common antibiotics such as oxacillin and amoxicillin. Furthermore, *mecA* also provides general resistance to many β-lactam antibiotics, such as the penicillins. Moreover, SCC*mec* elements may also contain genes responsible for resistance to a wide array of antimicrobials besides β-lactams.

Emergence of CA-MRSA and LA-MRSA

While MRSA infections were observed sporadically in the community among individuals who had had recent exposure to health-care settings or had been in close contact with MRSA-infected individuals,[15] MRSA was considered to be primarily a health-care-associated threat until the late 1990s. At that time, a dramatic shift in the MRSA target population occurred, as otherwise healthy individuals in the community developed MRSA infections in quickly increasing numbers.[2,16–18] The first case of community-associated MRSA (CA-MRSA) was reported in 1993 in a remote part of Western Australia lacking any close health-care facility.[19] Shortly thereafter, CA-MRSA appeared in the US, causing the deaths of four children in the Upper Midwest region.[20,21] The history of the onset of CA-MRSA in the US has been reviewed elsewhere in great detail,[2,5,16,17] and thus will not be the subject of further discussion here. Currently, a persistently high number of CA-MRSA infections are being observed, in particular in the US, but also in increasing frequency in other parts of the world, reaching pandemic proportions.[16,22,23] The fact that the CA-MRSA epidemic is particularly severe in the US is likely due to the high pathogenic potential of the US epidemic CA-MRSA strain USA300, which is now also spreading to other countries. The superiority of USA300 over other CA-MRSA strains may be due to a specific MGE, termed arginine catabolic mobile element (ACME), which harbors genes involved in pathogen survival on the human skin.[24,25]

Hospital-associated (HA-) and CA-MRSA are defined based on their distinctive association with the hospital or community settings, respectively. According to the current definition, CA-MRSA infections are those for which the onset of infection is within 48 hours of admission to the hospital with no previous history of hospitalization in the past year, whereas HA-MRSA is defined by the onset of infection occurring after 48 hours of hospital admission.[26] The successful transfer of strains from the hospital to the community and vice versa has occurred, leading to "community-acquired hospital onset" and "hospital-acquired community onset" MRSA infections.[27,28] For that reason, some authors have suggested that CA-MRSA cannot be clearly distinguished anymore from HA-MRSA.[29] However, one has to be aware that the CA-/HA-MRSA definition is clinical, not microbiological. While specific strains are typically associated with CA-MRSA infections, the mere identification of the infective isolate as, for example, USA300 does not make an infection a CA-MRSA infection.

At present, an increasing number of reports from the US and abroad indicate that CA-MRSA strains are gradually replacing HA-MRSA strains in hospitals. Several authors have suggested that this indicates yet another potential epidemiological shift in staphylococcal infections.[30–32] Nevertheless, the traditional hospital-associated strains, such as those of the USA100 and USA200 lineages, are still highly prevalent in hospitals, indicating that they are well adapted to that setting.[33,34]

S. aureus has also long been associated with severe infections in a variety of economically important livestock animals, including poultry, pigs, and cattle.[35–38] MRSA in particular has been increasingly associated with livestock-associated (LA-MRSA) infections over the last 40 years.[39–42] Although MRSA strains caused widespread infections among livestock animals, they showed distinct host tropism.[43,44] However, the notion that *S. aureus* strains have evolved to thrive within a single species[45] was recently challenged by reports of LA-MRSA strains infecting livestock-associated workers,[46] human-to-poultry-transfer of sequence type (ST)-5 strains,[42] and transmission of such strains as USA100, USA300, and USA500 between humans and their companion animals.[47–53] Thus, the recent breach

of the genus barrier by LA-MRSA strains points towards remarkable host adaptability of LA-MRSA and indicates that livestock animals can serve as a reservoir for infections in humans.

Target population, transmission, and pathology of infection

S. aureus is a frequent asymptomatic colonizer of humans. Roughly a third of the human population carries *S. aureus*, primarily in the nose,[54,55] but also in other body parts, such as the nasopharynx, groin, and perineum.[56] The occurrence of MRSA colonization in the human population is estimated to be about 1.5%, of which roughly one in six carries a CA-MRSA strain.[57,58] Recent epidemiological data suggest that CA-MRSA carriage is on the rise in the human population.[59]

There are several risk factors for the acquisition of an MRSA infection. Generally, an individual is at high risk for infection from his or her own colonizing strain.[60] The transmission of the bacteria from an infected to a noninfected individual takes place either by direct skin-to-skin contact with an infected person or through contaminated fomites in public and household settings.[61,62] Poor personal hygiene and a compromised skin barrier are believed to play important roles in developing infection in the community, while underlying conditions such as a compromised immune system increase the risk for MRSA infection during hospitalization. MRSA is prevalent in health-care workers,[63] indicating that these workers might serve as a reservoir for the spread of HA-MRSA infections in hospitals. Close contact with infected livestock and companion animals is a direct cause of LA-MRSA infections in humans.[64,65]

The target population of MRSA infections is diverse. Groups at high risk for CA-MRSA infections include prison inmates, military personnel,[66] athletes,[62] intravenous drug users,[9] and men who have sex with men.[67] The elderly, children,[68] patients with indwelling medical devices,[69] people with underlying disease conditions such as diabetes[70] or neutrophil dysfunction,[71] HIV/AIDS patients,[72,73] and individuals who have had a recent history of influenza are at high risk primarily for HA-MRSA infection.

MRSA disease manifestations are equally diverse with regard to seriousness and scope. Mild-to-severe skin and soft-tissue infections are among the most common MRSA-related diseases.[74] However, serious medical complications, such as dermatitis,[75] osteomyelitis,[76] necrotizing pneumonia,[77] ventilator-associated pneumonia,[78] endocarditis,[79] and bloodstream infections (BSIs)[80] may be caused by MRSA. MRSA-related BSI is the highest cause of mortality in the US among bacterial BSI.[81] While most CA-MRSA infections are usually infections of the skin and soft tissues, CA-MRSA may also cause severe infections, such as necrotizing pneumonia or necrotizing fasciitis.[74] LA-MRSA infections in livestock animals include leg weakness in boiler chickens, abscess and septicemia in rabbits, dermatitis in pigs, and mastitis in cattle.[35,37,38,82]

Global epidemic status and economic burden

MRSA is the most prominent cause of nosocomial infections caused by a single bacterial pathogen in the US and many parts of the world.[27,83–85] It is estimated that about 44% of all hospital-associated infections can be attributed to MRSA.[86] Recent estimates suggest that in the US, the mortality due to MRSA infections is higher than that due to HIV/AIDS.[87]

The severity of infections caused by MRSA is thought to be higher than that caused by methicillin-sensitive *S. aureus* (MSSA),[88] not because MRSA strains are in general more virulent, but because they offer fewer therapeutic options. Mounting evidence suggests that MRSA infections lead to a longer stay in hospitals, which in turn leads to higher costs.[89,90] According to recent estimates, general MRSA infections resulted in 1 million extra days of hospitalization in the EU, corresponding to US$570 million of additional costs.[86] In the US, the cost per MRSA infection is thought to be $12,000,[86,91] and a delay in the diagnosis of MRSA bacteremia attributes to costs ranging between $3,800 and $27,000 per patient.[92,93] Furthermore, MRSA-related cases of osteomyelitis,[94] outbreaks in neonatal intensive care units,[95] and infections of indwelling medical devices[96] appear to be on the rise in hospitals.

CA-MRSA is a significant public health threat[97] and considered to be the most frequent cause for visits to emergency rooms in the US.[98] Currently, CA-MRSA is endemic in Sri Lanka, Taiwan, People's Republic of China, the Philippines, Vietnam, Australia, Greece, and the UK, besides the US.[4,26,99] Worldwide, most CA-MRSA cases are mild soft-tissue infections, although requirement for hospitalization due to severe adult cases of community-associated skin and soft-tissue infection (SSTI) remains high and is estimated to be between 16% and 44%.[100] SSTIs are increasing in frequency in the US,[101] mostly because of CA-MRSA and the recurrent nature of CA-MRSA infections.[102] Of note, SSTI can serve as a source of BSI and hence higher health-care-related cost per patient.[80]

Current treatment of MRSA

The treatment of MRSA infections is becoming increasingly more complicated due to increasing resistance to antimicrobials and strain diversity. Thus, treatment of MRSA infections is gradually getting geared towards personalized therapy.

In general, therapy for serious MRSA infections involves a multistep process. At first, debridement of the infecting MRSA strain is required, which includes drainage of the contaminated tissue or removal of the infected medical device. Prompt debridement or removal of the infection foci improves the outcome[103,104] and prevents the relapse of infection.[104,105] Along with debridement, laboratory tests are performed on the infecting bacterial strain to determine its antibiogram (ie, antibiotic susceptibility). The antibiogram dictates the type of antimicrobial therapy. The Infectious Disease Society of America (IDSA) has set forth a detailed methodological guideline for clinical care of MRSA infections.[106]

Due to their efficiency, β-lactams are the antibiotics of first choice for staphylococcal infections. However, with MRSA rates becoming increasingly higher and less than 5% of clinical strains being sensitive to penicillins,[4] the treatment of *S. aureus* infection now relies increasingly on non-β-lactam-based antibiotics.[107] Although vancomycin is inferior to β-lactam drugs[108] in terms of potency in sterilizing the blood,[109,110] and toxic effects to kidneys,[111] it is the preferred drug for the treatment of MRSA infections.[112] Unfortunately, resistance to vancomycin already exists. According to the Clinical and Laboratory Standards Institute, vancomycin-sensitive *S. aureus*, vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA) are defined by bacterial inhibition at doses of <4 mg/mL, 4–8 mg/mL, and ≥ 16 mg/mL, respectively.[113,114] While VRSA has remained very rare, VISA is on the rise in the US.[115,116] High-level resistance to vancomycin in VRSA is due to the acquisition of the *vanA* gene,[117] while intermediate resistance is multifactorial and due to genetic alterations that increase the thickness of the cell wall.[118]

Apart from vancomycin, linezolid, daptomycin, and tigecycline are FDA-approved and effective against MRSA infections.[100,119] Notably, daptomycin is ineffective against pulmonary infections.[120] In addition, improved β-lactams such as cephalosporins (ceftaroline/ceftobiprole), carbapenems, long-acting tetracyclines (doxycyclines/minocyclines), clindamycin, rifampin, and improved glycopeptides (telavancin) are used to treat mild-to-severe MRSA infections, either alone or in combination therapies.[121–123]

The therapy to be used against an MRSA infection is often determined by the nature and severity of the infection. In cases of mild CA-MSRA skin infections, inexpensive oral agents are recommended. Clindamycin and doxycycline are good choices in this regard,[124,125] and are recommended in children with mild CA-MRSA-associated SSTI infections.[126] For less severe bacteremia or endocarditis, vancomycin together with a semisynthetic penicillin is the treatment of choice. When the infecting isolate shows a resistance level to vancomycin of >1 mg/mL or in cases of renal failure, daptomycin or linezolid are recommended. Linezolid is particularly favorable in cases of ventilator-associated and hospital-associated pneumonia.[127] The IDSA set forward clear guidelines for the treatment of MRSA infections. Vancomycin/daptomycin is the preferred drug for bacteremia and endocarditis, vancomycin/daptomycin along with rifampin for prosthetic valve infections, and vancomycin/linezolid/clindamycin for HA/CA-MRSA pneumonia.

The drugs currently used to treat MRSA infections are progressively showing decreasing efficacy due to increasing bacterial resistance. Several cases of *S. aureus* resistance to "last-resort drugs," such as vancomycin, daptomycin, and linezolid, have been reported,[128–131] which calls for the development of new and improved anti-MRSA drugs. Several new drugs are under development, such as carbapenems (cefonicid, ceftazidime), quinolones, and glycopeptides (dalbavancin, oritavancin).[132] Unfortunately, vaccine-intervention strategies against *S. aureus* have failed so far. An alternative vaccine approach targeting virulence determinants has gained momentum in recent times. Staphylococcal α-toxin, Panton–Valentine leukocidin (PVL), leukocidin ED, and the recently described phenol-soluble modulin (PSM) transporter could serve as potential targets for such an approach (see below).

MRSA typing

There has been a persistent effort to understand the epidemiology of *S. aureus* by typing the infective isolates, for which a number of molecular methods are currently in practice.[12,133] While all methods provide valuable information regarding staphylococcal phylogeny, some are predominantly directed to decipher bacterial microevolution, such as multilocus sequence typing (MLST) and staphylococcal protein A (spa) gene typing, whereas others, such as pulsed-field gel electrophoresis (PFGE) and SCC*mec* typing, yield more information about large genetic changes, such as gene deletions or duplications.

MLST is based on the sequence analysis of 450-base-pair internal fragments of seven housekeeping genes. Isolates showing sequence similarity in all seven genes are given

a unique ST number, and closely related STs are grouped together in a single clonal complex (CC). Spa typing is based on the sequencing of the polymorphic X region of the *spa* gene.[134] Both MLST and spa typing are currently centralized and automated (for MLST, http://saureus.mlst.net; for spa typing, http://www.egenomics.com or http://spaserver.ridom.de).

PFGE is the analysis of DNA fragments following *Sma*I digestion of the bacterial genome on an agarose gel. PFGE is highly reliable and a gold standard for strain designations.[135] However, low portability of data along with regional description of PGFE patterns (in the US, USA100 or USA200 etc; in Australia, WMRSA; in the UK, EMRSA; and in Canada, CMRSA) make it difficult to compare isolates.

SCC*mec* is an MGE of 21–67 kb in length that contains the *mecA* gene. Currently, there are eleven different allotypes of SCC*mec* – types I–XI (http://www.sccmec.org) among *S. aureus* strains – of which SCC*mec* type III is the largest and SCC*mec* type IV the smallest. Due to its smaller size, SCC*mec* IV is thought to give a fitness advantage compared to other SCC*mec* types.[136,137]. Usually HA-MRSA isolates carry SCC*mec* types I, II, or III, whereas CA-MRSA isolates possess SCC*mec* types IV, V, or VII.[138]

Epidemiology of MRSA epidemic waves

S. aureus infection rates rise and fall in epidemic waves. Epidemic waves are rapid and widespread outbursts of *S. aureus* infections affecting many individuals in an area or population. The causes underlying the appearance and disappearance of *S. aureus* epidemics are largely unknown, but likely comprise exposure to a new antibacterial agent, or in some cases lifestyle habits.[2]

Epidemic wave 1 (1950s, phage type 80/81, penicillin-resistant strains)

This first recorded outbreak was caused by penicillin-resistant strains of the phage type 80/81 lineage, following the introduction of penicillin in the 1940s. It started in the UK, and in the 1950s had become a worldwide problem.[139]

Epidemic wave 2 (1960s, archaic MRSA)

This outbreak was due to the spread of the first MRSA clones, shortly following the introduction of methicillin. It caused mostly serious health-care-associated infections, but also occasionally mild community-associated infections throughout Europe.[11]

Epidemic wave 3 (1980s, toxic-shock syndrome clones)

Toxic-shock syndrome (TSS), also referred to as staphylococcal scarlet fever, was first reported in 1978 among young menstrual women.[140] The following years saw a severe outbreak of TSS cases, with the use of superabsorbent tampons soon discovered to be the underlying risk factor.[141] The exotoxin encoded by the *tst* gene was identified as the single molecular determinant of TSS.[142]

Epidemic wave 4 (1980s until present, HA-MRSA)

This outbreak followed the rise of a novel MRSA lineage, called Iberian or Rome clone, which became pandemic in the hospitals. Several other strains of *S. aureus*, such as USA100, USA200, EMRSA-15, and EMRSA-16, emerged as further common HA-MRSA strains and continue to cause a high number of nosocomial infections worldwide.[2,143,144]

Epidemic wave 5 (1990s until present, CA-MRSA)

This epidemic started in Western Australia with the discovery of the first case of CA-MRSA caused by the WA-1 or WA-MRSA1 strain. A close relative of the WA-1 strain, the USA400 strain, soon became widespread in the US and Canada.[19,145] This epidemic wave constitutes two overlapping waves, the first of which was prevalent until 2001 and caused by the USA400 strain. This was followed by the current CA-MRSA pandemic caused by the USA300 strain. Currently, USA300 is the major cause of CA-MRSA infections in many countries, including the US,[146] while infections due to USA400 strains are restricted mainly to Alaska and the Pacific Northwest.[2]

Epidemic wave 6 (early 2000s LA-MRSA outbreak)

This outbreak in humans is caused by a pig-associated MRSA isolate of the CC398 lineage. LA-MRSA was first reported in Europe, but is currently pandemic and can sometimes cause serious infections among healthy livestock workers and veterinarians. The LA-MRSA pandemic exemplifies a rare but increasingly occurring case of shared infection between animals and humans.[29,30]

Worldwide emergence of epidemic MRSA strains

The majority of MRSA infections are caused by strains belonging to a few CCs. The most prevalent are CC1 (USA400), CC5

(USA100 or NY/Japan clone, USA800 or pediatric clone), CC8 (Col, Iberian clone, USA300, and USA500), CC22 (EMRSA-15), CC30 (USA200, EMRSA-16, USA1100, the Southwest Pacific Oceania clone), CC45 (USA600, Berlin clone), CC59 (Taiwan), and CC80 (Europe).[2,133] Of these, CCs 1, 5, 8, 22, 30, and 45 are prominent in the hospitals, whereas CCs 1, 8, 22, 30, 59, and 80 are mostly prevalent in the community. MRSA strains representing CCs 8 and 30 are pandemic both in the hospitals and in the community, and are among the most frequently isolated strains from infections. CC 22 and 30 represented by ST22 (EMRSA-15) and ST36 (EMRSA-16) strains are prevalent in the UK. All known VISA strains belong to CC5. The archaic and Iberian MRSA, USA400, and USA300 strains belong to CC8. Of note, these representative CCs are not exclusive to MRSA, but also include MSSA strains. For example, the phage type 80/81strains discussed above belong to CC30. Finally, there are some regional clones, such as ST772 (Bengal Bay clone), which is mostly prevalent in Bangladesh and India,[147] ST72 strains in South Korea, the Caribbean, and Portugal, and ST88 strains in Africa and Asia.[133,148,149]

Emergence and dominance of USA300 in current CA- and HA-MRSA infections

USA300 has emerged as the dominant CA-MRSA strain in the US.[31] First isolated in 2000, it was traditionally a community-associated strain,[150] but it now also represents a major threat to patients in hospitals and long-term care facilities.[32,151] Additionally, USA300 is increasingly responsible for the majority of CA-MRSA infections worldwide, including in Canada, Europe, Australia, Japan, and Latin America.[146,152–154]

Consistent with USA300's global dominance, laboratory experiments show elevated virulence of this strain compared to contemporary MRSA isolates.[155,156] Notably, the USA300 strains in the US are highly clonal and closely genetically related.[157] While the evolution of CA-MRSA virulence, and in particular that of USA300, is a matter of ongoing debate,[18] the enormous success of USA300 is attributed generally to increased resistance of USA300 to antimicrobial agents,[67,158,159] increased expression of virulence genes[156] and their regulators, higher persistence,[25] and acquisition of virulence determinants on MGEs, such as PVL[160] (see below).

Recent emergence of LA-MRSA

The first case of LA-MRSA was reported in 1972 in cows.[41] LA-MRSA is associated with a relatively small number of lineages. For example, bovine infections are caused predominantly by strains belonging to CC97, CC126, CC130, and ST151. CC398 and ST9 are predominantly present in pigs. The isolation of a novel *mecA* gene ($mecA_{LGA251}$), also known as *mecC*,[161] from cattle suggests that LA-MRSA strains are distinct from HA- and CA-MRSA. Recently, bovine-specific LA-MRSA strains were isolated from humans in the UK, Denmark, and Germany,[162] suggesting that cows can serve as a reservoir for human MRSA. Subsequently, several cases of LA-MRSA-mediated human infections were reported throughout the world. The underlying risk factor for these infections is primarily exposure to livestock.[40]

CC398 was first discovered in Europe in early 2000 and rapidly became the major cause of human LA-MRSA infections. Studies performed in Denmark and Belgium showed that livestock-associated veterinarians have a high chance of being infected by CC398 LA-MRSA strains.[163] Presently, CC398-mediated LA-MRSA infections have reached pandemic proportions, as several cases have been reported from such geographically diverse locations as Canada, China, Colombia, and the Caribbean.[148,164,165] In the Netherlands, human cases of CC398 infections represent 25% of total MRSA infections.[166] Pigs are thought to be the major asymptomatic carriers of CC398 clones[167]; however, CC398 strains have also occurred in cows, veal, poultry, horses, and dogs.[46] CC398 clones show high diversity.[168] Interestingly, cases of CC398 MSSA strains colonizing healthy individuals have been reported in the US.[169] Recent research indicates that the CC398 LA-MRSA strains may have been derived from a human MSSA CC398 isolate that was transferred to pigs, where it obtained the SCC*mec* cluster.[168]

Evolution of MRSA pathogenic success

The success of *S. aureus* as a pathogen is to a large extent due to its ability to resist antimicrobial agents and circumvent the immune surveillance of the host. Many molecular determinants of resistance and virulence in *S. aureus* are encoded on MGEs. The presence of those factors is thus highly strain-dependent, while some core genome-encoded virulence determinants are present in virtually all strains.

The commonly MGE-encoded determinants of antimicrobial resistance have already been discussed in previous sections. In addition, *S. aureus* possesses an enormous repertoire of virulence and persistence genes that may be genome- or MGE-encoded. In this article, only a selected few are presented. The reader is referred to review

articles presenting the molecular basis of *S. aureus* virulence in more detail.[18,170]

The core genome-encoded pore-forming toxin, α-toxin, is produced by most *S. aureus* strains. α-Toxin is proinflammatory, shows cytolytic effects to various immune cells except human neutrophils,[171] and is critical for *S. aureus* virulence in various animal models of infection.[172,173] Vaccination with a nontoxic α-toxin variant provides protection against staphylococcal pneumonia and skin infection.[174,175]

PSMs are a group of small, core genome-encoded amphipathic peptides of ~20–45 amino acids. They are present in all *S. aureus* strains and considered key determinants in the development of skin, bloodstream, and biofilm-associated infections.[176,177] In particular α-type PSMs are strongly cytolytic toward neutrophils and erythrocytes at the micromolar range.[176] Notably, PSMα peptides of *S. aureus* destroy neutrophils after phagocytosis from within the neutrophil phagosome.[178,179] At nanomolar concentrations, all PSMs are proinflammatory by receptor-mediated interaction.[176,180] The PSM-secretion machinery in *S. aureus* has recently been identified,[179] potentially representing a target for simultaneous interference with all PSMs.

Leukotoxins are perhaps the most extensively studied staphylococcal virulence determinants in recent times. Clinical strains of *S. aureus* may produce four different types of bicomponent leukotoxins, namely PVL, γ-hemolysin, leukotoxin ED, and/or leukotoxin AB/GH.[181] Apart from γ-hemolysin, they are all MGE-encoded.[182] All leukotoxins are proinflammatory and show cytolytic activity towards neutrophils, with considerable host specificity.[183–186] Recently, the CCR5 receptor was shown to recognize leukotoxin ED,[187] suggesting that in contrast to previous belief, the cytolytic activities of – possibly all – staphylococcal leukotoxins are receptor-dependent.

ACME harbors a set of genes that enable the bacteria to utilize arginine present on human skin to their metabolic advantage and detoxify host-derived antimicrobial agents.[24,25] Of note, ACME, likely acquired from *S. epidermidis*, is exclusively present in the USA300 background among *S. aureus* strains, potentially explaining the superiority of USA300 over other CA-MRSA strains.

Current efforts in understanding molecular MRSA epidemiology

There has been a recent emphasis on understanding MRSA epidemic waves on the molecular level. In a rare effort to combine epidemiological and functional analyses for that purpose, an *S. aureus* MGE-encoded factor, the surface protein SasX, was identified to be significantly increasing in frequency among Asian HA-MRSA strains. Notably, SasX was found to be associated with increased nasal colonization, immune evasion and virulence.[188] Furthermore, genome comparison of the pandemic phage type 80/81 strain with that of a contemporary CC30 HA-MRSA strain showed that a truncated α-toxin gene and mutated *agrC* led to a reduction in aggressive virulence in the contemporary HA-MRSA CC30 background, possibly explaining the success of those clones in the hospital environment.[189] Further genome-wide studies were recently performed to document the evolution of bacterial resistance to vancomycin and linezolid within patients during antimicrobial therapy.[190–193] Several longitudinal studies with isolates from cystic fibrosis,[194] persistent infections in households,[195] and an MRSA clone before and after BSI[196] revealed several subtle genetic changes compromising virulence, cell-wall biosynthesis, and antimicrobial resistance. All these studies suggest that minor genetic adaptations may contribute to the development of MRSA fitness and persistence.

Current surveillance efforts

Active surveillance of MRSA with guidelines for proper treatment and documentation of hospital-associated MRSA cases is performed in many countries. The so-called search-and-destroy approach to deal with MRSA cases is practiced in many parts of Europe, including the Scandinavian countries and the Netherlands. It involves the routine screening of patients and health-care personnel for MRSA, and has proved to be highly successful.[197,198] Because poor hygiene correlates with a higher prevalence of MRSA, and improper use of antibiotics with a higher MRSA carriage,[199] the control of MRSA includes cost-effective sanitizing methods, such as proper hand-washing and an overall restrained use of antibiotics. Recent clinical data show that HA-MRSA cases have been on a decline in the US between 2005 and 2008[200] and in the UK since 2006, probably due at least in part to these measures, and in the latter case the mandatory surveillance of MRSA.[201,202]

Concluding remarks

Half a century after its surge, MRSA remains a serious threat to public health-care systems worldwide. MRSA strains have gained resistance to a variety of antibiotics, and an *S. aureus* vaccine is not available or in sight. Owing to the low fitness cost associated with methicillin resistance and the relatively easy transmission from infected individuals or fomites, the bacteria can spread easily. The surge in global travel over

the last few decades has added to the spread of MRSA. It is now a generally accepted view that proper management of the MRSA problem needs a multipronged approach. This approach should include global surveillance of MRSA, development of new and improved antimicrobial agents, and increased understanding of MRSA pathophysiology through basic scientific research.

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