

Methicillin-resistant *Staphylococcus aureus*: an overview of basic and clinical research

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Abstract | Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most successful modern pathogens. The same organism that lives as a commensal and is transmitted in both health-care and community settings is also a leading cause of bacteraemia, endocarditis, skin and soft tissue infections, bone and joint infections and hospital-acquired infections. Genetically diverse, the epidemiology of MRSA is primarily characterized by the serial emergence of epidemic strains. Although its incidence has recently declined in some regions, MRSA still poses a formidable clinical threat, with persistently high morbidity and mortality. Successful treatment remains challenging and requires the evaluation of both novel antimicrobials and adjunctive aspects of care, such as infectious disease consultation, echocardiography and source control. In this Review, we provide an overview of basic and clinical MRSA research and summarize the expansive body of literature on the epidemiology, transmission, genetic diversity, evolution, surveillance and treatment of MRSA.

Endocarditis

An infection of the interior heart structures or valves.

Osteomyelitis

An infection involving bone.

Methicillin

An anti-staphylococcal penicillin.

Fomite

An object or material capable of carrying or transmitting infection.

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First identified in purulent fluid from a leg abscess by Ogston in the 1880s and formally isolated by Rosenbach not long after, *Staphylococcus aureus* is well adapted to its human host and the health-care environment¹. *S. aureus* is both a frequent commensal and a leading cause of endocarditis, bacteraemia, osteomyelitis and skin and soft tissue infections. With the rise of hospital-based medicine, *S. aureus* quickly became a leading cause of health-care-associated infections as well. Penicillin offered short-lived relief: resistance arose in the 1940s, mediated by the β -lactamase gene *blaZ*. The first semi-synthetic anti-staphylococcal penicillins were developed around 1960 and methicillin-resistant *S. aureus* (MRSA) was observed within 1 year of their first clinical use. In fact, genomic evidence suggests that methicillin resistance even preceded the first clinical use of anti-staphylococcal penicillins². Methicillin resistance is mediated by *mecA* and acquired by horizontal transfer of a mobile genetic element designated staphylococcal cassette chromosome *mec* (SCC*mec*)³. The gene *mecA* encodes penicillin-binding protein 2a (PBP2a), an enzyme responsible for crosslinking the peptidoglycans in the bacterial cell wall. PBP2a has a low affinity for β -lactams, resulting in resistance to this entire class of antibiotics⁴.

MRSA was first observed among clinical isolates from patients hospitalized in the 1960s, but since

the 1990s it has spread rapidly in the community⁵. Although MRSA infection occurs globally, there is no single pandemic strain. Instead, MRSA tends to occur in waves of infection, often characterized by the serial emergence of predominant strains. Recent examples of emergent MRSA strains include the health-care-associated MRSA (HA-MRSA) clonal complex 30 (CC30) in North America and Europe, community-associated MRSA (CA-MRSA) USA300 in North America and livestock-associated MRSA (including ST398) and ST93 in Australia^{6–9}. Rates of both CA-MRSA and HA-MRSA appear to be declining in several regions, a trend first noted with HA-MRSA in the United Kingdom^{10,11}. The reason for the serial rise and fall of specific strain types remains poorly understood.

MRSA colonization increases the risk of infection, and infecting strains match colonizing strains in as many as 50–80% of cases^{12,13}. Nearly any item in contact with skin can serve as a fomite in MRSA transmission, from white coats and ties to pens and mobile telephones. Colonization can persist for long periods of time. MRSA may also persist within the home environment, complicating attempts at eradication¹⁴. At the same time, colonization is not static, as strains have been found to evolve and even to be replaced within the same host¹⁵.

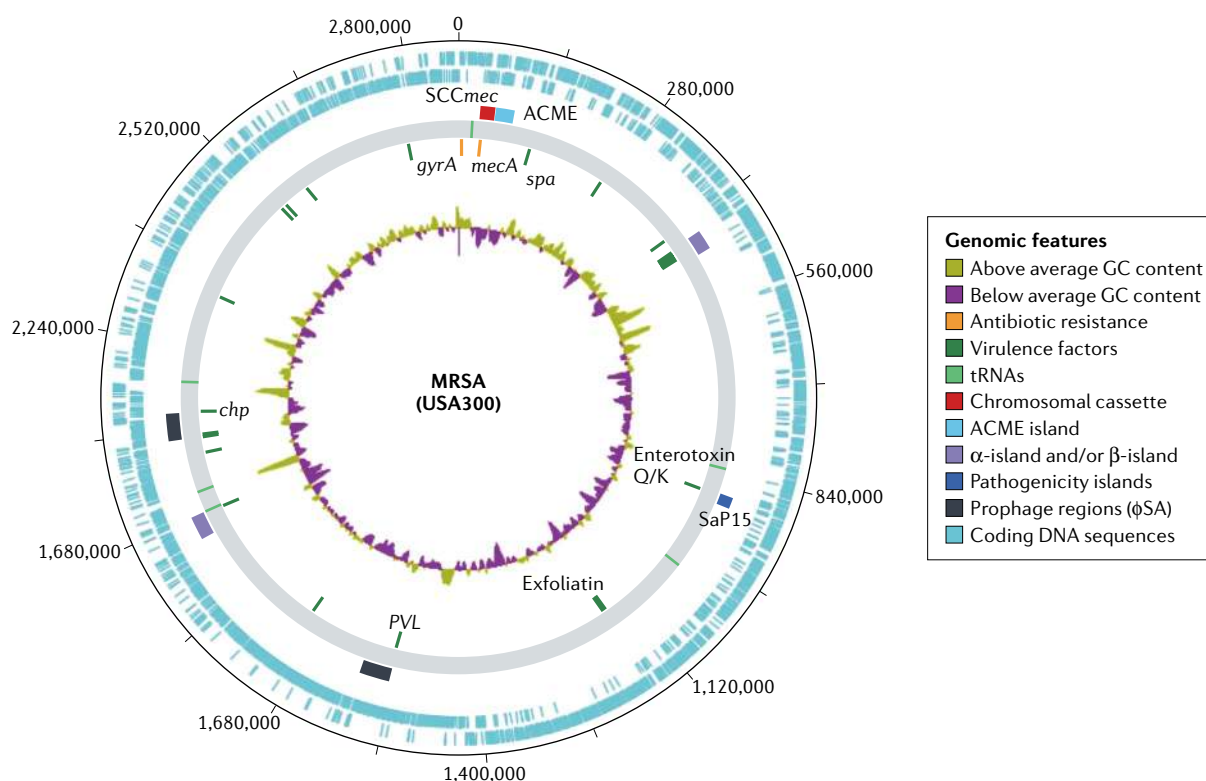


Fig. 1 | Major genomic elements in methicillin-resistant *Staphylococcus aureus*. Representative genomic map of the USA300 strain FPR3757 (REF.⁷⁷). The innermost circular track (track 1) represents GC content. Moving outwards, track 2 displays select antibiotic resistance genes in orange and virulence factors in green. Track 3 shows the location of tRNAs. Track 4 displays select mobile genetic elements, with chromosomal cassettes in red, various pathogenicity islands in shades of blue through violet and prophages in black. The outer two tracks (5 and 6) represent coding sequences in blue. PVL, Pantón–Valentine leukocidin. Selected annotation created using Artemis/DNAPlotter¹⁶⁶. MRSA, methicillin-resistant *Staphylococcus aureus*.

As MRSA can infect nearly any body site, effective management is best determined by the site of infection. There are well-proven roles for echocardiography and infectious disease consultation (that is, evaluation by a physician with subspecialty training in infectious diseases) in *S. aureus* bacteraemia. Several novel antimicrobials have recently been developed against MRSA and are in various stages of clinical trials, including cefaroline, ceftobiprole, dalbavancin, oritavancin, iclaprim and delafloxacin^{16–19}.

Even with the ongoing development of new antibiotics, active surveillance efforts and advances in infection prevention, MRSA remains a prominent pathogen with persistently high mortality. The advent of antibiotics reduced *S. aureus* bacteraemia mortality from 80% to a still unacceptable 15–50%²⁰. Massive research efforts continue to expand our understanding of the genetic diversity, epidemiology, evolution and management of MRSA. In this Review, we examine key topics that underpin our understanding of MRSA, including its clinical and molecular epidemiology, the influence of evolution and genetic diversity on the transmission of MRSA, and its treatment.

Evolution and genetic diversity

Bacterial genomes are broadly divided into core and accessory components. The core genome refers to those genes present in all isolates (generally containing

essential genetic information related to cellular metabolism and replication). The core comprises ~75% of the 2.8 Mb genome of *S. aureus* and is highly conserved among strains²¹. Much of the genetic diversity of MRSA and other pathogens occurs within the accessory genome, where mediators of virulence, immune evasion and antibiotic resistance are commonly found. The accessory component comprises ~25% of the total *S. aureus* genome. It consists of mobile genetic elements (MGEs) such as pathogenicity islands, bacteriophages, chromosomal cassettes, transposons and plasmids, which are acquired by horizontal transfer between strains (FIG. 1; TABLE 1). Consequently, the accessory genome tends to be more variable and often more strain-specific than the core genome.

The gain and loss of virulence determinants carried on MGEs have a vital role in bacterial adaptability, virulence and survival. For example, MRSA is defined by the presence of the 20–65 kb *SCCmec* element inserted within the *orfX* (an RNA methyltransferase) gene of *S. aureus*²². *SCCmec* contains the *mecA* gene complex (responsible for methicillin resistance) and a set of site-specific recombinase genes (*ccrA* and *ccrB*) that are responsible for its mobility. Over 90% of known *S. aureus* genomes can be categorized into just four predominant clonal complexes (CC5, CC8, CC398 and CC30), which are closely related families of strain types as defined by multilocus sequence typing (see TABLE 2 for

Echocardiography

A diagnostic imaging technique in which ultrasound is used to construct images of heart chambers, valves and associated structures.

Mobile genetic elements

Segments of DNA-encoding enzymes that mediate transfer of DNA within and between bacterial genomes.

Table 1 | Selected major genomic elements in Methicillin-resistant *Staphylococcus aureus*

Category	Gene name	Gene product	Function	Location
Antibiotic resistance	<i>aacA-aphD</i>	Bifunctional AAC-APH protein	Aminoglycoside resistance	Transposon
	<i>aadD</i>	Aminoglycoside adenylyltransferase	Aminoglycoside resistance	Plasmid
	<i>ant</i> (4')	O-nucleotidyltransferase(4')	Aminoglycoside resistance	• SCCmec • Plasmid
	<i>ant</i> (9)	O-nucleotidyltransferase(9)	Aminoglycoside resistance	Transposon
	<i>blaZ</i>	β -Lactamase	Penicillin resistance	• Plasmid • Transposon
	<i>bleO</i>	Bleomycin binding protein	Bleomycin resistance	• SCCmec • Plasmid
	<i>cat</i>	Chloramphenicol acetyltransferase	Chloramphenicol resistance	Plasmid
	<i>dfrA</i> and <i>dfrK</i>	Dihydrofolate reductase	Trimethoprim resistance	Plasmid
	<i>ermA</i>	rRNA methylase	Macrolide resistance	Transposon
	<i>ermC</i>	rRNA methylase	Macrolide, lincosamide and streptogramin resistance	Plasmid
	<i>ileS</i>	Isoleucyl-tRNA synthetase	Mupirocin resistance	Plasmid
	<i>mecA</i>	Penicillin-binding protein 2	Methicillin resistance	SCCmec
	<i>tetK</i>	Tetracycline resistance protein	Tetracycline resistance	Plasmid
	<i>tetM</i>	Tetracycline resistance protein	Tetracycline resistance	Transposon
Antiseptic or heavy metal resistance	<i>arsRBC</i>	Efflux ATPase	Heavy metal resistance	Plasmid
	<i>cadA</i> and <i>cadB</i>	Cadmium efflux ATPase	Heavy metal resistance	Plasmid
	<i>qacA</i>	Antiseptic resistance protein qacA	Antiseptic efflux pump	Plasmid
	<i>merA</i> and <i>merB</i>	Mercuric reductase	Heavy metal resistance	Transposon
Virulence factors ^a	<i>aur</i>	Aureolysin	Tissue destruction	Core
	<i>capA</i> and <i>capP</i>	Capsular polysaccharide biosynthesis proteins	Immune evasion	Core
	<i>chp</i>	Chemotaxis inhibitory protein	Immune evasion	Bacteriophage
	<i>clfA</i> and <i>clfB</i>	Fibrinogen binding proteins	Adhesion	Core
	<i>coa</i>	Staphylocoagulase	Coagulation	Core
	<i>ebhA</i> and <i>ebhB</i>	Extracellular matrix-binding proteins	Adhesion	Core
	<i>eta</i>	Exfoliative toxin A	Scalded skin syndrome	Plasmid
	<i>etb</i>	Exfoliative toxin B	Scalded skin syndrome	Bacteriophage
	<i>etd</i>	Exfoliative toxin D	Scalded skin syndrome	vSAy
	<i>geh</i>	Lipase	Lipid degradation	Core
	<i>hld</i>	δ -Haemolysin	Haemolysis	Core
	<i>hlgA</i> , <i>hlgB</i> and <i>hlgC</i>	γ -Haemolysin components	Haemolysis	Core
	<i>hysA</i>	Hyaluronidase	Tissue invasion	vSa β
	<i>lukD</i> and <i>lukE</i>	Leukotoxins	Immune evasion	SaPI
	<i>lukS-PV</i> and <i>lukF-PV</i>	Panton-Valentine leukocidin	Leukotoxin	Bacteriophage
	<i>sak</i>	Staphylokinase (protease III)	Clot dissolution	Bacteriophage
	<i>sea</i>	Enterotoxin A superantigen	Food poisoning	Bacteriophage
	<i>seb</i> and <i>sec</i>	Enterotoxin B and enterotoxin C (superantigens)	Food poisoning	SaPI
	<i>seq2</i> and <i>sek2</i>	Enterotoxin and superantigen	Food poisoning	SaPI
	<i>sep</i>	Enterotoxin P	Food poisoning	Bacteriophage
	<i>spa</i>	Immunoglobulin G-binding protein A	Immune evasion	Core
	<i>sspA</i>	Serine protease	Tissue destruction	Core
	<i>sspB</i>	Cysteine protease	Tissue destruction	Core
	<i>tst</i>	Toxic shock syndrome toxin 1	Superantigen	SaPI

List compiled from REFS^{26,77,177,178}. rRNA, ribosomal RNA; SaPI, *Staphylococcus aureus* pathogenicity island. ^aNot a comprehensive list.

Table 2 | Overview of techniques used for molecular characterization of *Staphylococcus aureus*

Technique	Methodology	Advantages	Disadvantages
Pulsed-field gel electrophoresis	DNA is fragmented by restriction enzymes, and the resulting fragments are then separated by an electric field that periodically changes direction ¹⁷⁹	Highly discriminatory, widely available and relatively low cost	Laborious, technically challenging, interlaboratory variability, not well suited for long-term or global epidemiology ¹⁸⁰
MLST	Comparison of partial sequences from seven housekeeping genes; alleles for each are defined by a standardized MLST database, and strains are defined by particular combinations of alleles ¹⁸¹	Highly discriminatory and reproducible, well suited to long-term global epidemiology; eBurst algorithm was designed and validated for use with MLST data ¹⁸²	Expensive and laborious
Spa typing	Sequence-based analysis of 24 bp variable number tandem repeats 3' of polymorphic X or the short sequence repeat region of the <i>spa</i> gene; sequences are referenced to one of two large international databases (Ridom or eGenomics) ¹⁸³	Rapid and well suited to outbreak investigations	Moderately expensive (though less costly than MLST)
Multilocus variable number of tandem repeat analysis	DNA profiling by assessment of variation in number of tandem short repeat sequences ¹⁸⁴	High-throughput and inexpensive	Newer technique with variable protocols; discriminatory power yet to be well evaluated
SCCmec typing	PCR-based technique in which unique SCCmec types are assigned to particular allotypes of the <i>ccr</i> and <i>mecA</i> genes	Less expensive than MLST or whole genome sequencing	Use confined to MRSA; divergent and evolving SCCmec types have been discovered that are not detected by current methods ¹⁸⁵
Repetitive element palindromic PCR	PCR fingerprinting method targeting repetitive DNA sequences scattered throughout the MRSA genome	Inexpensive, commercially available, easy to use and rapid	Less discriminatory — perhaps most suitable for initial screening ¹⁸⁶
Whole genome sequencing	Analysis of entire genome sequence for single-nucleotide variants ¹⁸⁷	Precise and highly discriminatory	Expensive; extensive data analysis and knowledge of bioinformatics required
STAR gene restriction profile analysis	STAR is PCR amplified and then digested with restriction enzymes to produce restriction profiles that vary based on variation in sequence and copy number of intergenic regions within the PCR product ¹⁸⁸	Rapid, easy to perform and reproducible	Discriminatory power varies by enzymes used — may be better suited for initial screening ¹⁸⁹

MLST, multilocus sequence typing; SCCmec, staphylococcal cassette chromosome *mec*; STAR, *Staphylococcus aureus* repetitive element.

a summary of techniques used to define MRSA strain types²³. This pattern suggests that the horizontal acquisition of SCCmec has occurred on a limited number of occasions among relatively few predominant strain types. However, at least one episode of horizontal transfer of SCCmec has been observed during an epidemic²⁴. In addition to SCCmec, most MRSA strains contain at least one temperate bacteriophage. Transducing phages can carry up to 45 kb of bacterial host DNA and are likely responsible for the majority of horizontal transfers of MGEs between *S. aureus* strains²⁵.

Drug resistance. MGEs carrying antibiotic resistance genes have been acquired by MRSA on multiple independent occasions. Resistance to penicillin (*blaZ*), trimethoprim (*dfrA* and *dfrK*), erythromycin (*ermC*), clindamycin (constitutively expressed *ermC*) and tetracyclines (*tetK* and *tetL*) have all been identified on insertion sequences, transposons and sometimes plasmids in both MRSA and methicillin-susceptible *Staphylococcus aureus* (MSSA)²⁶. Likely reflecting the strong selective pressures within the hospital environment, antibiotic resistance is often genetically linked to disinfectant or heavy metal resistance (for example, quaternary ammonia compounds, mercury or cadmium) among HA-MRSA strains²⁷.

The emergence of resistance to vancomycin is the most feared genetic adaptation in *S. aureus* to date, given the widespread reliance on this antibiotic in treating MRSA infections, and illustrates how both core and accessory genomic components uniquely influence the acquisition of antibiotic resistance. *S. aureus* exhibits two forms of vancomycin resistance. Vancomycin-intermediate *S. aureus* (VISA) strains tend to emerge with prolonged or repeated courses of vancomycin treatment. Within a population, multiple different mutations confer differing degrees of vancomycin resistance — a trait termed heteroresistance. Time and sustained selective pressure (for example, prolonged vancomycin therapy) select for strains that have gradually accumulated multiple mutations and successively higher vancomycin minimum inhibitory concentrations (MICs). This phenomenon has been confirmed through the repeated whole genome sequencing of isolates with steadily rising vancomycin MICs, some accumulating over 30 different mutations²⁸. The majority of mutations documented in VISA isolates alter core genome components of cell wall biosynthesis and autolysis. Several such mutations, including those in *ycyH*, *mprF* and *dltA*, also confer cross resistance to daptomycin^{28,29}. In contrast to VISA, high-level vancomycin-resistant *S. aureus* has been shown to occur through plasmid transfer of the *vanA* operon

Clindamycin

An antibiotic in the lincosamide family.

Methicillin-susceptible *Staphylococcus aureus* (MSSA). *Staphylococcus aureus* strains that are susceptible to methicillin, oxacillin and cefoxitin.

Minimum inhibitory concentrations

(MICs). The lowest concentration of a chemical at which bacterial growth is prevented.

Competent

Refers to bacteria capable of taking up DNA from their environment for recombination.

Hyaluronidase

An enzyme that catalyses the degradation of hyaluronic acid; it may play a role in pathogenesis by facilitating the breakdown of host intercellular matrix.

Arginine-catabolic mobile element

(ACME). A mobile genetic element that accompanies staphylococcal cassette chromosome *mec* (SCC*mec*) and is believed to have a role in the regulation of growth and survival in *Staphylococcus aureus* and strain fitness.

Panton–Valentine leukocidin

(PVL). A cytotoxin produced by some strains of *Staphylococcus aureus* that induces pore formation in the membranes of white blood cells, resulting in cell lysis.

***att*_s sites**

Sites targeted by the staphylococcal cassette recombinases.

Gene nurseries

Regions of the genome from which other genes are believed to have originated.

Phenol-soluble modulins

(PSM). A peptide toxin that attracts and lyses white blood cells.

from vancomycin-resistant *Enterococcus faecalis*³⁰. Of note, MRSA is not naturally competent, and conjugative plasmids are rare — thus, most plasmid transfer in MRSA occurs through transduction. Fortunately, this appears to be a rare occurrence with few cases of vancomycin-resistant *S. aureus* reported to date³¹.

Virulence factors. *S. aureus* expresses a wide range of virulence factors, including toxins (haemolysins and leukocidins), immune-evasive surface factors (for example, capsule and protein A) and enzymes that promote tissue invasion (for example, hyaluronidase). One challenge in analysing the success of strains from dominant clonal complexes stems from the fact that successful lineages often differ from their predecessors at multiple loci. USA300 from CC8 has been especially well studied in this regard. Relative to USA500, another variant within CC8, USA300 has multiple additional virulence determinants acquired through MGEs. Two of the most studied are the arginine-catabolic mobile element (ACME) and Panton–Valentine leukocidin (PVL). The acquisition of ACME is largely restricted to USA300, and it preceded the rapid spread of this strain. It is posited to improve survival in the low-pH environment found on skin³². The role for PVL, encoded in prophage Sa2int, has proved more controversial. Despite a mechanistic role in neutrophil lysis and an apparent association with necrotizing pneumonia and soft tissue infection, subsequent studies in both animals and humans indicate that PVL is neither the sole nor primary determinant of MRSA infection severity³³.

The *S. aureus* pathogenicity islands (SaPIs) are another group of accessory genes ranging from 14 to 17 kb in size. SaPIs generally contain two or more superantigen genes, such as those for toxic shock syndrome toxin 1 (TSST1) and enterotoxin types B and C, associated with toxic shock syndrome and food poisoning, respectively. SaPIs are mobilized in extremely high frequency following infection by certain bacteriophages and are integrated into one of six specific *att*_s sites on the staphylococcal chromosome, always in the same orientation²⁶.

Genomic islands and ‘gene nurseries’ are another key determinant of MRSA genetic diversity. Three families of genomic islands have been reported: *vSA* α , *vSA* β and *vSA* γ . Each is flanked by a truncated transposase gene upstream and a partial restriction-modification system type I downstream. Genomic islands exhibit substantial interstrain variety but tend to be very stable once acquired by horizontal transfer. Genomic islands carry a range of virulence factors including superantigens, lipoproteins, proteases, leukocidins, hyaluronidases and b-type phenol-soluble modulin (PSM) genes^{21,26}.

Multiple other toxins active against the human host (for example, exfoliative toxins, adhesins and haemolysins) have been reported in a wide array of MGEs within the MRSA genome. Although much attention is focused on toxins active against the host, bacteriocins are other MGE-transferrable toxins that MRSA may use to inhibit competing or commensal bacteria²⁶.

Despite the prominent role of MGEs, they are not the only means by which MRSA adapts to its host. Mutations within the core genome are known to alter

the expression of several key virulence factors, including cytolytic phenol-soluble modulins and α -toxin. Differential expression of the regulatory component *agr* has been positively correlated with PSM and α -toxin expression in both USA300 and USA500 strains, potentially influencing the success of USA300 (REF.³⁴).

With expansive sources of genetic variation, the potential for emergence of novel MRSA clones is theoretically quite high. Fortunately, we have yet to see an isolate that has amassed all the major virulence and antibiotic resistance factors known to date. Bacterial defence mechanisms, such as the restriction-modification system and CRISPR, have evolved to protect against foreign DNA and likely limit what would otherwise be prolific genetic exchange³⁵. Genome-level research into MRSA MGEs is revealing the complexity of MRSA evolution, in which the prevalence, gain and loss of particular MGEs vary over time, likely influenced by selective pressures balanced against fitness cost³⁶.

Epidemiology

Risk of MRSA infection is elevated among children, elderly individuals, athletes, military personnel, individuals who inject drugs, persons with an indigenous background or in urban, underserved areas, individuals with HIV or cystic fibrosis, those with frequent health-care contact and those in institutionalized populations, including prisoners^{37–40}. Rates of MRSA infection increased rapidly between the 1990s and early 2000s. Since 2005, parallel decreases in MRSA infections have been confirmed in multiple US and European populations, especially among bloodstream and soft tissue infections^{10,41–44}. Paediatric trends mirror those seen in adults in the United States⁴⁵. Although specific factors responsible for the changing rates of MRSA infection remain uncertain, advances in molecular epidemiology are informing an increasingly complex understanding of MRSA population dynamics.

Between the first reports of MRSA in 1961 and in the 1990s, infection was generally associated with health-care contact. By the 1990s, cases of MRSA infection emerged in individuals who had no prior hospitalization, leading to separate definitions for HA-MRSA and CA-MRSA. CA-MRSA isolates were initially distinguished by lower rates of clindamycin resistance (particularly in the United States), increased likelihood of PVL expression, a predominance of SCC*mec* type IV or type V and strain types ST5 or ST8 (REFS^{3,46}). However, since the 1990s, genotypic differences by site of acquisition have begun to homogenize, demonstrating that CA-MRSA and HA-MRSA can each invade the other's niche⁴⁷.

The molecular epidemiology of *S. aureus* is largely characterized by the successive emergence of regionally predominant strain types. Penicillin-resistant phage type 80 or type 81 of *S. aureus* surged between 1953 and 1963. After originating in hospitals, it spread to communities in North America, the United Kingdom and Australia before inexplicably receding again⁴⁸. With the emergence of MRSA in the 1960s, HA-MRSA began to affect hospitals in North America, the United Kingdom, Australia and Japan while spreading in the Scandinavian countries

One Health approach

An integrative approach to medicine that recognizes connections between animal, environmental and human health.

to a lesser extent. Sporadic reports of MRSA occurring without prior health-care contact began to appear in the 1980s and 1990s, just before the widespread emergence of regionally dominant CA-MRSA strains.

Perhaps the most infamous of these strains, USA300 (an ST8 or CC8 derivative), rapidly overtook other circulating strain types as a dominant cause of CA-MRSA skin and soft tissue infections across the United States in 2000 (REF.⁴⁹). Some of the earliest cases of USA300 arose with an outbreak of CA-MRSA skin infections among a group of football players in Pennsylvania, followed shortly thereafter by a similar cluster in a Mississippi prison, establishing the first epidemiologic associations between MRSA, athletes and those in prisons^{50,51}. As USA300 spread, it also proved capable of causing invasive infection at a wide range of body sites, perhaps most notably necrotizing pneumonia following influenza virus infection⁵². In contrast to its rapid spread across North America and despite multiple introductions into other continents, USA300 has not achieved the same dominance globally⁵³. Although it has become regionally established across the globe in several countries outside of North America, emerging evidence suggests that the total burden of infection from USA300 is finally beginning to slow or even decline in parallel with an overall decrease in MRSA incidence rates^{54,55}. It is worth noting that a parallel CA-MRSA epidemic occurred in South America with the related strain USA300-LV (Latin American variant), though this strain appears to have arisen from a common ancestor rather than by direct spread of USA300 (REF.⁵⁶).

Other well-described MRSA strain types show similar patterns of regional epidemic spread. Unlike USA300 in North America, however, MRSA isolates exhibit greater genetic diversity globally (FIG. 2). Epidemic methicillin-resistant *S. aureus* 15 (EMRSA-15) ST22 (CC22) and EMRSA-16 ST36 (CC30) emerged as predominant HA-MRSA strain types in the United Kingdom in the late 1990s^{57–59}. The same strain types, ST22 and ST30, predominate among HA-MRSA isolates in continental Europe⁶⁰. ST30 (CC30) has also successfully spread through the Asia-Pacific regions and parts of the Americas^{48,61,62}. Beyond the wide spread of CC30 strains, this particular clonal complex has been associated with relatively higher invasive infection rates and mortality⁶³. The ST22 strain appears to be gradually overtaking ST239, another widely distributed HA-MRSA strain (from CC8) that has been found in Europe, the Middle East, Asia and the Pacific^{64,65}. European CA-MRSA exhibits a fair amount of diversity, though ST80 has been well described in parts of western Europe with some spread to northern Africa and the Middle East^{59,64,66}. Just as USA300 has achieved only limited spread beyond the United States, even relatively successful European strains, such as ST30, ST22 and ST80, remain rare in the United States⁸.

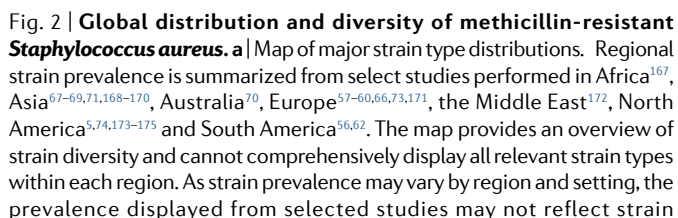
Strain maps of isolates from Asia and the Pacific are especially diverse, with ST72 (CC8) well described in Korea, ST8 or ST30 in Japan, ST59 in Taiwan, and greater diversity still in China^{61,67–69}. ST93 is well described as a major cause of CA-MRSA skin and soft tissue infections specifically among indigenous populations

in central Australia, whereas ST772 (the Bengal Bay clone) has spread from its namesake Bay of Bengal in the Indian Ocean to parts of Pakistan and Nepal, confirming the ongoing emergence of distinct, regionally predominant clones^{70,71}.

The One Health approach has also drastically informed MRSA epidemiology with the recognition of CA-MRSA transmission between livestock and humans^{9,72}. ST398 (CC398) has been well reported as a cause of livestock-associated CA-MRSA in Europe since 2005 (REF.⁷³). ST398 has since been confirmed as a cause of livestock-associated CA-MRSA also in Asia, Australia and the Americas, though it is not the only strain to occur in livestock^{69,74}. Interspecies transmission may impose additional evolutionary constraints on MRSA, as particular genetic markers associated with immune evasion, such as *scn*, *chp* and *sak*, appear to exhibit divergent selection, being positively correlated with human infection but negatively associated with livestock colonization⁷⁵.

Insights from genomics. One interesting feature of MRSA epidemiology is that despite substantial overall diversity, relatively few strains dominate. Whole genome sequencing has allowed the reconstruction of the spread of MRSA within both health-care systems and communities. Phylogenetic reconstructions from whole genome sequencing data of CA-MRSA isolates confirm that USA300 emerged through rapid clonal expansion rather than convergent evolution⁶. Whole genome sequencing has even provided sufficient resolution to determine that household clustering (for example, co-occurrence of multiple cases of MRSA infection within one familial dwelling) likely had a substantial role in the transmission of USA300 within the community^{32,76}. Similarly, detailed phylogenetic reconstructions suggest that individuals colonized by circulating community strains subsequently introduced USA300 into hospitals, resulting in the eventual intermixing of CA-MRSA and HA-MRSA strains⁴⁷.

Modern genomic approaches have provided new insights into the factors driving the emergence and spread of successful CA-MRSA strains. Subsequent attempts to identify the factors responsible for the success of USA300 identified multiple candidates, broadly categorized into MGEs and core genome components. Early attention focused on MGEs. Whole genome sequencing of USA300 isolates quickly identified multiple MGEs carrying a range of virulence factors (including PVL) and drug resistance determinants. Among these, the arginine-catabolic mobile element (ACME) appeared unique to USA300. One of the key enzymes in the arginine catabolism pathway, arginine deiminase, inhibits innate and adaptive immune responses and improves pathogen survival. By increasing the expression of multiple genes within this pathway, ACME was hypothesized to increase the fitness of USA300 relative to other *S. aureus* strains⁷⁷. However, further genome-level comparative studies demonstrated that MGEs do not explain the entirety of the success of USA300. Instead, it seems that upregulation of the virulence regulatory gene *agr* mediates increased expression of PSMs



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and α -toxin, correlating with increased virulence in USA300 independent of any MGEs^{34,78}.

Genomic methods have also helped to map the spread of HA-MRSA across the globe, exemplified by the story of HA-MRSA in the United Kingdom. EMRSA-16 (CC30) was the predominant HA-MRSA strain in the United Kingdom beginning in the 1990s, before being overtaken by EMRSA-15 (CC22) in the early 2000s⁵⁹. As with CA-MRSA, whole genome sequencing permitted the detailed tracking of the spread of each strain. EMRSA-16, for example, appears to have spread from major urban centres, such as London and Glasgow, outwards to regional and local hospitals — likely carried by patients transferring from one facility to another⁷. Acquisition of antimicrobial resistance (particularly to fluoroquinolones and antiseptics, such as quaternary ammonia compounds) correlates with the spread of EMRSA-16, linking strain success to an ability to survive strong selective pressures within the health-care environment where antibiotics and antiseptics are commonplace. A remarkably similar series of events was seen with the successor of EMRSA-16, EMRSA-15 (ST22), which has since spread beyond the United Kingdom to other parts of Europe, Asia, Australia and Africa. EMRSA-15 has also acquired resistance to additional antibiotics as it has spread — again likely contributing to its success in the highly selective hospital environment. Although many antibiotic resistance markers appear to have been acquired on multiple occasions, fluoroquinolone resistance is the most stable and consistent trait among successful isolates⁷⁹.

Drastic shifts in epidemiology rarely arise as a result of a single genetic trait, however, and more recent analysis suggests that at least some of the clonal expansion of HA-MRSA preceded the widespread acquisition of fluoroquinolone resistance^{32,54,79}.

Additionally, there is emerging evidence that declining HA-MRSA infection rates are strain-specific and preceded the deployment of enhanced infection control and antibiotic stewardship measures in the United Kingdom¹¹. This pattern suggests that selection pressures imposed by human efforts have been less influential than originally thought. Although genomics has substantially expanded our understanding of MRSA epidemiology, the factors contributing to the success of particular strains are not fully understood. It is likely that strain dominance results from the complex interplay of both genetic adaptations and host genetic variability and from the broader context shaped by the environment, health-care practices and social and geographic factors.

Colonization and transmission

S. aureus colonizes the nares of 28–32% of the US population. MRSA nasal colonization rates range from 0.9% to 1.5% in the United States⁸⁰. Elevated risk of colonization mirrors risk of infection as noted above: athletes, those in prisons, military recruits, children, persons in urban, underserved areas, individuals with an indigenous background, pet owners, livestock workers, individuals with prior MRSA infection, individuals with

HIV or cystic fibrosis and individuals with frequent health-care contact are all at increased risk of MRSA colonization^{37,40,81–85}. Recent receipt of antibiotics has also been associated with elevated risk of MRSA carriage⁸¹. Determining exactly how long colonization persists is challenging, though some have observed MRSA persistence greater than 6 months after initial infection or contact with MRSA⁸⁶. MRSA has also been readily recovered from a variety of fomites, including household environments, phones, pagers, notebooks, ties, pens, white coats, gloves and isolation gowns. This environmental persistence makes durable decolonization of MRSA difficult and is likely to contribute to the well-documented transmission of MRSA between household contacts⁸⁷.

Although rates vary by study, colonizing strains genetically match infecting strains in as many as 50–80% of individuals, and MRSA colonization may increase infection risk by as much as 25%^{12,13,88}. In particular, the presence of staphylococcal enterotoxin P has been correlated with increased risk of bacteraemia in individuals in which it has colonized⁸⁹. Interestingly, colonization appears to be dynamic, as different strain types can be isolated from different body sites, and colonizing strains have been observed to switch between methicillin-resistant and susceptible phenotypes over time^{15,90}. Particular strains of *Staphylococcus epidermidis* that secrete the serine protease Esp also appear to inhibit *S. aureus* biofilm formation and may decrease the risk of MRSA colonization⁹¹.

As MRSA is both a commensal and pathogen, there is active interest in whether detection of MRSA colonization followed by an attempt to eliminate carriage can reduce the risk of subsequent infection. Multiple studies have attempted to define optimal approaches for screening and decolonization (TABLE 3). Traditionally, MRSA colonization was detected by swabbing the nares, though subsequent research with different screening methods and at various body sites showed the sensitivity of traditional nasal swab screening to be as low as 66%⁹². PCR-based methods offer the highest sensitivity overall, though at a higher cost and with some reported risk of false positive results^{93,94}. For example, false positive results have been reported for PCR kits that target SCC, as a subset of MSSA strains carry an SCC lacking *mecA*⁹⁴. Interestingly, even the type of swab used seems to influence identification: sponges or swabs with nylon-flocked tips outperform traditional rayon swabs⁹⁵. In addition to the nares, MRSA colonization has been detected in oropharyngeal, axillary, perineal, rectal, perirectal and even intestinal samples^{96–99} (FIG. 3). Perirectal colonization is especially pertinent for the population of men who have sex with men. Among individuals admitted to intensive care units (ICUs), rates of tracheal colonization may even exceed those for nares. Screening of multiple body sites has also been shown to improve detection, with most studies reporting the screening of 2–3 sites as optimal for detection^{100–103}. In summary, although no single combined technique has been thoroughly assessed, PCR-based screening from multiple body sites appears to offer the highest overall sensitivity for detecting MRSA carriage.

Table 3 | Impact of screening and decolonization on the development of methicillin-resistant *Staphylococcus aureus* infections

Study design	Study setting	Screening	Intervention	Decolonization	Study outcomes	Impact on study outcomes	Refs
Retrospective cohort single centre, n = 6,864	Cardiac surgery ICU (United States)	• Sites: nares • Timing: pre-admission • Test: PCR	USC, TD	MU, CH, OT ^a	MRSA SSI	Reduced colonization	109
Cluster-randomized trial multicentre, n = 74,256 ^b	ICU (United States)	• Site: nares • Timing: variable ^c • Test: culture	USC, TI, UD, TD	MU, CH	ICU-attributable MRSA BSI	No effect	111
Cluster-randomized crossover trial multicentre, n = 7,735	ICU and bone marrow transplant unit (United States)	–	UD	CH	Hospital-acquired MRSA BSI	No effect	112
Quasi-experimental pre and post multicentre, n = not available	Veteran Affairs acute health-care facilities (United States)	• Site: nares • Timing: at admission • Test: culture or PCR	USC, TI	OT ^d	Health-care-associated MRSA infections	Reduced colonization	106
Quasi-experimental pre and post multicentre, n = 5,043	ICU (United States)	–	UD	CH	MRSA BSI	No effect	190
Retrospective cohort multicentre, n = 933	Hospital (United States)	• Site: nares • Timing: at admission • Test: culture and PCR	USC, TD	MU, CH	MRSA infection	No effect	107
Prospective interventional cohort single centre, n = 21,754	Surgery (United States)	• Sites: nares, perineum • Timing: pre-admission or at admission • Test: PCR	USC, TI, TD	MU, CH, OT ^{a,e}	Health-care-associated MRSA infection and MRSA SSI	No effect	108
Observational cohort study multicentre, n = 153,340	Hospital (United States)	• Site: nares • Timing: at admission • Test: PCR	USC, TI, TD	MU, CH	Health-care-associated MRSA infection and MRSA BSI	Reduced colonization	191
Observational cohort study single centre, n = 1,462	Cardiac surgery (United Kingdom)	• Site: nares • Timing: at admission • Test: PCR	USC, TD	MU, OT ^{a,f}	MRSA SSI	Reduced colonization	110

–, not tested or studied; BSI, bloodstream infection; CH, chlorhexidine; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; MU, mupirocin; OT, other; SSI, surgical-site infection; TD, targeted decolonization; TI, targeted isolation; UD, universal decolonization; USC, universal screening. ^aAdjustment in perioperative antibiotic prophylaxis. ^bThree-group study: group 1 (USC and TI); group 2 (USC, TI and TD); group 3 (UD). ^cBilateral nares screening on admission for groups 1 and 2 only. ^dHand hygiene and change in institutional culture. ^eComputerized MRSA alert system. ^fTopical triclosan for 5 days.

At the public health level, the Netherlands and Nordic European countries have employed a ‘search and destroy’ policy relying upon the identification of MRSA carriage among both patients and health-care personnel, strict isolation of individuals positive for MRSA, elimination of carriage where feasible and proactive management of outbreaks¹⁰⁴. Although multiple factors may contribute to low rates of MRSA carriage and infection in these countries, the search and destroy approach appears effective where resources are sufficient to support its use. As an example, Denmark successfully used this strategy to limit the spread of a CA-MRSA clone (ST30) in the early 2000s¹⁰⁵.

The management of MRSA colonization continues to evolve. Infection prevention measures, including screening, contact isolation and good hand-hygiene practices, show mixed results when applied individually but have reduced infection rates as much as 40–60% when combined^{106–108}. Targeted decolonization efforts have similarly decreased surgical-site infections in patients receiving cardiac surgery^{109,110}. The REDUCE trial showed benefit for universal decolonization in an ICU setting, and daily

chlorhexidine bathing has also been shown to reduce the risk of multidrug-resistant infection during hospitalization^{111,112}. Topical nasal mupirocin alone previously failed to reduce subsequent MRSA infection risk, perhaps owing to colonization at other body sites, thus leading other researchers to advocate for chlorhexidine bathing or even systemic antibiotics in decolonization protocols^{107,113}. Further research is required to define best approaches for persistent carriers, high-risk surgical groups (for example, recipients of prosthetic devices), efficacy of different decolonization strategies and decolonization protocols specific to perianal carriers and oral carriers.

Treatment

Approved antibiotics for MRSA vary by clinical indication. Despite the prevalence and severity of MRSA infections, there is a relative paucity of high-quality randomized controlled trials (RCTs) to guide therapy for all indications except acute bacterial skin and skin structure infections (ABSSSIs). TABLE 4 offers a concise summary of currently available clinical data for antibiotics with activity against MRSA.

Mupirocin

A topical antibiotic with activity against *S. aureus*.

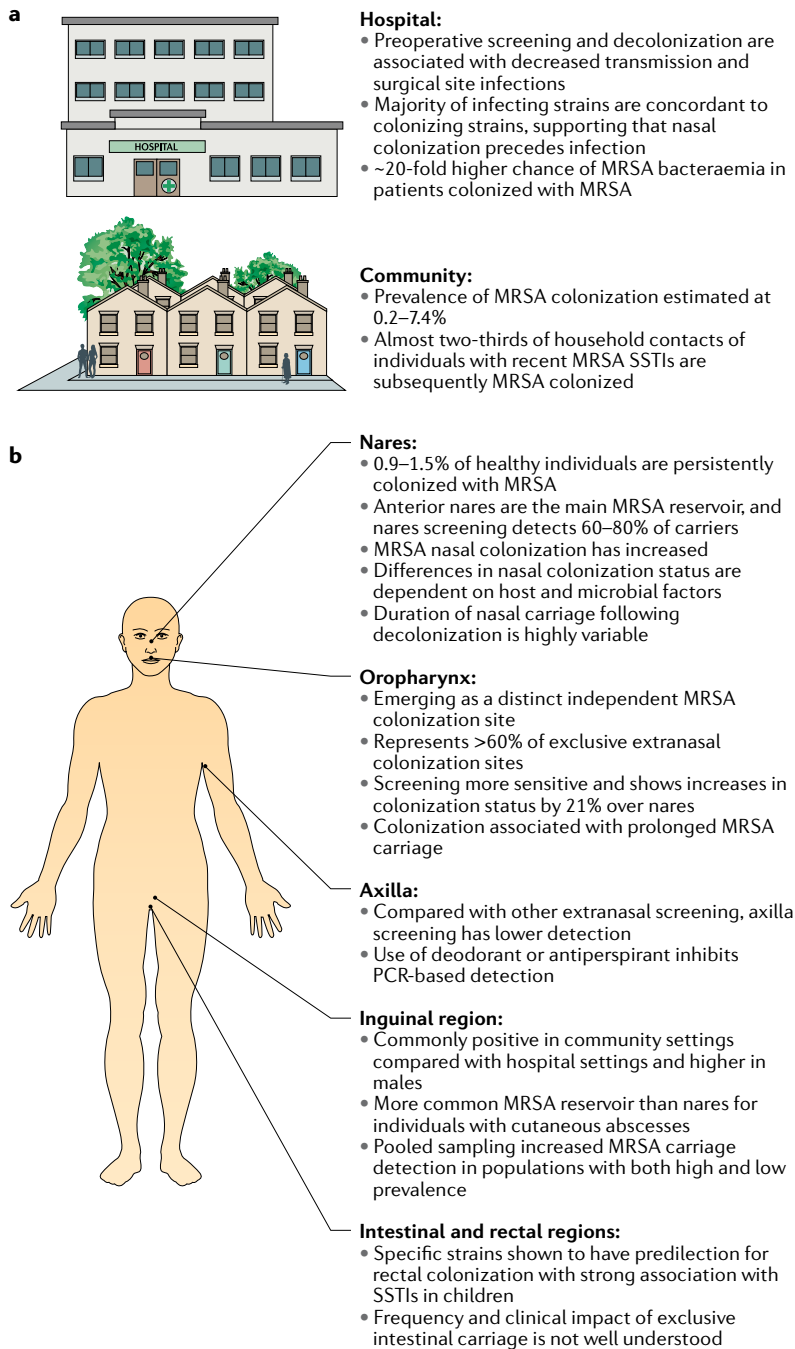


Fig. 3 | Methicillin-resistant *Staphylococcus aureus* colonization. **a** | Impact of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization on hospital-acquired infection and community transmission. **b** | MRSA screening by anatomic site. Swab culture of nares is the most standard and widely used method for detecting MRSA carriers; however, recent data have shown that extranasal colonization is frequent. Extranasal MRSA screening increased MRSA detection by one-third over that detected by MRSA nares screening alone, indicating that sole assessments of MRSA nasal carriage are not sufficient. ICU, intensive care unit; SSTI, skin and soft tissue infection.

Transoesophageal

A technique for echocardiography in which the echo probe is positioned within the oesophagus, providing much higher resolution imaging of select heart structures.

Bacteraemia and endocarditis. Nearly all patients with MRSA bacteraemia should be assessed for endocarditis, with transoesophageal echocardiography preferred over transthoracic echocardiography as the more sensitive test. Various prediction rules have been developed to identify the limited subset of patients at sufficiently low risk of endocarditis to forego transoesophageal

echocardiography. These prediction tests generally pertain to nosocomial bacteraemia among patients who exhibit rapid clearance of blood cultures, no clinical signs of endocarditis or secondary foci of infection and absence of haemodialysis or indwelling intracardiac devices¹¹⁴. For decades, vancomycin has been the first-line therapy for MRSA bacteraemia and infective endocarditis¹¹⁵. However, dosing can be challenging, varying by weight and renal function while carrying a risk of nephrotoxicity¹¹⁶. Additionally, vancomycin may become less effective when the MIC approaches 2 mg/l, a somewhat controversial phenomenon known as ‘MIC creep’, which refers to the observation that vancomycin MICs have gradually increased over time, a trend that has been inconsistently associated with reduced treatment efficacy even while an isolate may still remain technically susceptible to vancomycin¹¹⁷.

Daptomycin, proven non-inferior to vancomycin in an RCT, is the only other FDA-approved first-line agent for MRSA bacteraemia or right-sided endocarditis¹¹⁸. Importantly, because daptomycin is inactivated by pulmonary surfactant, it should not be used in the treatment of MRSA bacteraemia secondary to pneumonia¹¹⁹. The emergence of daptomycin-nonsusceptible MRSA strains has been well described, particularly in association with inadequate source control, persistent MRSA bacteraemia, subtherapeutic dosing and extensive prior courses of vancomycin^{120,121}. Telavancin and dalbavancin have been evaluated in phase II RCTs^{122,123}. Linezolid has been associated with increased mortality relative to that with vancomycin in the treatment of catheter-related bloodstream infections, though this may have been due to confounding by the presence of concomitant Gram-negative infection within the linezolid group. At least by modified intention-to-treat analysis (including only patients with Gram-positive bacteraemia), linezolid was non-inferior¹²⁴. Published experience with ceftaroline in MRSA bacteraemia or endocarditis is currently limited to case series and retrospective cohort studies of salvage therapy¹²⁵.

Data supporting combination therapy are limited. Although the CAMERA1 trial found a decreased duration of bacteraemia with a combination of vancomycin and flucloxacillin compared with vancomycin monotherapy, it was intended as a proof-of-principle study¹²⁶. A follow-up CAMERA2 trial was terminated in December 2018 by recommendation of the Data Safety Monitoring Committee¹²⁷. The recent ARREST trial convincingly demonstrated that adjunctive rifampin has no role in MRSA bacteraemia or native valve endocarditis¹²⁸. The role of adjunctive therapy in MRSA prosthetic valve endocarditis is unknown, as few patients with a prosthetic valve were included in ARREST. Adjunctive gentamicin therapy for MRSA bacteraemia and native valve endocarditis is associated with an increased risk of harm (nephrotoxicity) without an accompanying improvement in mortality^{129,130}.

Current guidelines recommend treating 4–6 weeks from first negative blood culture for complicated MRSA bacteraemia and 6 weeks for endocarditis. Uncomplicated MRSA bacteraemia is an increasingly uncommon designation, as it requires endocarditis to be absent, no implanted prostheses, MRSA undetectable

Table 4 | Summary of antibiotics active against methicillin-resistant *Staphylococcus aureus*

Antibiotic	FDA-approved indications	Off-label use	Ongoing clinical trials	Comments
Vancomycin	Bacteraemia, pneumonia, osteoarticular infection, ABSSSI	–	–	–
Clindamycin	–	ABSSSI ¹⁹² Osteomyelitis ¹⁴⁸ Pneumonia ^{138,193}	–	–
Daptomycin	Bacteremia ¹¹⁸ , ABSSSI ¹⁹⁴	Osteomyelitis ¹⁹⁵	–	Daptomycin is inactivated by lung surfactant and is contraindicated in the treatment of pneumonia. May cause elevated creatine kinase
Linezolid	Pneumonia ¹³⁹ , ABSSSI ¹⁹⁶	Catheter-related MRSA bacteraemia ¹²⁴	–	Can lead to myelosuppression and neurotoxicity with prolonged therapy
Tedizolid	ABSSSI ¹⁹⁷	–	Osteoarticular infection ¹⁴⁷ Nosocomial pneumonia ¹⁹⁸	Lower incidence of thrombocytopenia and gastrointestinal side effects compared to linezolid
Trimethoprim with sulfamethoxazole	–	Uncomplicated ABSSSI ¹⁵⁵ Osteomyelitis	–	–
Ceftaroline	Pneumonia (only for community-acquired pneumonia — not MRSA pneumonia) ¹⁹⁹ , ABSSSI ²⁰⁰	Salvage therapy for bacteraemia and endocarditis ^{16,125,201,202}	Haematogenous osteomyelitis ²⁰³ Pneumonia ²⁰⁴ Bacteraemia ²⁰⁵	Ceftaroline has a similar, favourable side-effect profile as other cephalosporins
Ceftobiprole	–	Pneumonia ²⁰⁶ and complicated ABSSSI ²⁰⁷	Bacteraemia ²⁰⁸	Not available in the United States
Telavancin	Pneumonia ²⁰⁹ ABSSSI ²¹⁰	Bacteraemia ¹²²	Bacteraemia ²¹⁴	Telavancin resulted in more clinically significant creatinine elevations than standard therapy in the ASSURE trial. Bacteraemia trial ²¹⁴ discontinued by sponsor
Dalbavancin	ABSSSI ¹⁶¹	Catheter-related bloodstream infections ¹²³	Osteoarticular infections ²¹⁵	Once weekly dosing. Bacteraemia trial ²¹³ discontinued by sponsor
Oritavancin	ABSSSI ¹⁶⁰	–	–	Once weekly dosing
Delafloxacin	ABSSSI ¹⁸	–	Community-acquired pneumonia ²¹⁴	Well tolerated, minimal effect on QTc interval and cytochrome P450 enzyme
Quinupristin with dalbopristin	ABSSSI ²¹⁵	Pneumonia ²¹⁶	–	Requires central venous catheter for administration, high rate of infusion site reactions and adverse effects
Tigecycline	Pneumonia ²¹⁷ , ABSSSI ²¹⁸	Bacteraemia ²¹⁹	–	Tigecycline was associated with increased all-cause mortality in a meta-analysis of phase III and IV clinical trials; tigecycline should be used only when alternative treatment options are not available ²²⁰
Omadacycline	ABSSSI ¹⁵⁸	–	–	–
Alalevonadifloxacin	–	–	Phase I trials ^{221–224}	–
Brilacidin	–	–	ABSSSI ^{225,226}	–
Afabicin (Debio 1450)	–	–	ABSSSI ¹⁵⁹	–
Iclaprim	–	ABSSSI ^{156,157} , pneumonia ¹⁹	–	–

–, not tested or studied; ABSSSI, acute bacterial skin and skin structure infections.

Transthoracic

The standard, non-invasive method for echocardiographic imaging of the heart by applying the echo probe to the external chest wall.

from blood cultures within 2–4 days and no evidence of metastatic infection. Although the Infectious Diseases Society of America (IDSA) guidelines suggest patients with uncomplicated MRSA bacteraemia may be treated for 14 days, supporting data are limited¹³¹. A multi-centre RCT compared a treatment algorithm to standard treatment for staphylococcal bacteraemia. Compared

with standard treatment, algorithm-based treatment was non-inferior in regards to efficacy, resulted in no significant difference in safety and was associated with a 29% reduction in antibiotic usage in patients without complicated bacteraemia who could be evaluated¹³². Additionally, a trial investigating an early switch from intravenous to oral therapy is ongoing in Germany¹³³.

Non-inferior

In the specific context of clinical trials, a statistical definition by which an intervention is determined to be no worse than its comparator within a pre-specified range.

Pulmonary surfactant

A lipoprotein substance secreted by the lungs that reduces surface tension and thus prevents collapse of alveoli.

Modified intention-to-treat analysis

A variation on the traditional analysis of clinical trial results in which some subset of patients are excluded after randomization; there is no single definition for how this exclusion occurs, and there is some risk of introduction of bias.

Embolization

The occlusion of a blood vessel by a material travelling within the bloodstream; this may be caused by clot (that is, thrombus) or infectious material.

Pharmacokinetics

The study of the movement and distribution of medications within the body.

Myelosuppression

The inhibition of bone marrow activity resulting in decreased red blood cells, white blood cells and platelets.

Neuropathy

The dysfunction or disease of the peripheral nerves.

Two-stage exchange arthroplasty

A method of joint replacement in which the original infected artificial joint is removed in one operation, antibiotic treatment is given and re-implantation of a new artificial joint is performed at a later date.

Parenteral

Administered by a route other than the gastrointestinal tract; in general, refers to intravenous or injection therapies.

Haematogenous

Blood-borne or carried within the bloodstream.

In addition to appropriate antimicrobial therapy, infectious disease consultation reduces the mortality from MRSA bacteraemia¹³⁴. This improved outcome is likely due to, in part, the implementation of a variety of consultant-recommended quality practices, including increased use of echocardiography, follow-up blood cultures to ensure clearance and a thorough search for additional foci of infection potentially requiring surgical management¹³⁵.

American Heart Association guidelines recommend consideration of surgery for endocarditis with associated valve dysfunction (particularly if severe enough to cause heart failure), anatomic complications (such as valve perforations, heart block or perivalvular extension) or high risk of embolization. Most recommendations regarding the surgical indications and timing are based on either small observational studies or expert opinion¹³⁶. One RCT has been conducted to assess early versus delayed surgical management of infective endocarditis. It was not limited to endocarditis caused by *S. aureus*. As compared with conventional treatment, early surgery within 48 hours after randomization in patients with infective endocarditis and large vegetations significantly reduced the composite end point of death from any cause and embolic events by effectively decreasing the risk of systemic embolism¹³⁷. Decisions regarding surgical intervention for endocarditis remain complex, and a sufficiently detailed discussion of this topic is beyond the scope of this Review.

Pneumonia. Current American Thoracic Society and IDSA guidelines recommend vancomycin, linezolid or clindamycin for the treatment of MRSA pneumonia. The recommendation for clindamycin is based largely on a few small observational studies in children and a presumed benefit through reduced toxin production in PVL-positive strains¹³⁸. Linezolid exhibits excellent pulmonary pharmacokinetics and likely results in better clinical cure rates but has not shown a consistent decrease in mortality^{139–141}. Although ceftaroline is approved for the treatment of community-acquired pneumonia, few enrolled individuals had evidence of MRSA in sputum; thus, there is little published evidence to support its use in MRSA pneumonia¹²⁵.

Osteomyelitis. The propensity for *S. aureus* to form biofilms complicates the treatment of bone, joint and prosthetic-related infections. Vancomycin remains the first-line therapy despite poor bone penetration and failure rates as high as 35–46%¹⁴². Daptomycin is supported as an alternative agent by several retrospective studies^{143–145}. Linezolid is an appealing oral alternative, with nearly 100% bioavailability and excellent bone penetration, though prolonged use is associated with myelosuppression and neuropathy¹⁴⁶. Tedizolid may have fewer adverse effects than linezolid and is currently under investigation¹⁴⁷.

In paediatric patients, transition to oral clindamycin after initial intravenous therapy is generally accepted¹⁴⁸. In adults, initial treatment for MRSA osteomyelitis is generally administered intravenously

for at least the first 2 weeks¹⁴⁹. The optimal duration of treatment remains controversial, though in the specific case of MRSA vertebral osteomyelitis, durations less than 8 weeks may be associated with increased risk of recurrence¹⁵⁰.

Prosthetic joint infection. Prosthetic joint infections have been traditionally managed with two-stage exchange arthroplasty followed by 4–6 weeks of parenteral therapy. Although cure rates with the conventional two-stage therapy exceed 90%, a debridement and implant retention strategy has been suggested as an appropriate alternative for select patients with early acute haematogenous infection, a stable prosthesis, intact surrounding tissues and an isolate susceptible to rifampin^{151,152}. In the absence of any controlled trials, case series have reported various success rates, though one of the largest was only able to achieve a 55% cure rate with the debridement and implant retention strategy^{153,154}.

Skin and soft tissue infection. Incision and drainage should be performed whenever possible for purulent ABSSSIs. A recent large, placebo-controlled trial confirmed that antibiotic therapy reduces the likelihood of recurrent abscesses or treatment failure following incision and drainage¹⁵⁵. The number of antimicrobials approved to treat MRSA ABSSSIs is increasing with the recent approval of delafloxacin and omadacycline, two trials demonstrating efficacy for iclaprim, and active trials assessing afabacin (Debio 1450)^{18,156–159}. Two long half-life, single-dose injectable agents, oritavancin and dalbavancin, have also proved non-inferior to vancomycin^{160,161,162}.

Vaccine development

Attempts at vaccine development for MRSA have been disappointing to date. Three candidates have progressed to phase IIb/III trials. StaphVAX, a bivalent conjugate vaccine targeting capsular polysaccharides type 5 and 8, failed to induce durable immunity¹⁶³. V710, a monovalent vaccine targeting iron salvage protein IsdB, was actually associated with increased mortality, resulting in early termination of the trial¹⁶⁴. Most recently, Pfizer announced in December 2018 that the phase IIb trial of their multi-antigen vaccine (PF-06290510) was discontinued for futility¹⁶⁵.

Conclusions and outlook

MRSA is formidable, versatile and unpredictable. Its capacity for genetic adaptation and the serial emergence of successful epidemic strains cause it to remain a major threat to human health. Future efforts to understand MRSA should therefore focus on two areas. From a biological perspective, we need better insights into the complex interplay between host and pathogen. Studies that progressively evaluate genomics, epigenetics, transcription, proteomics and metabolomics in carefully selected animal models, and ultimately in clinically well-characterized patients with diverse forms of MRSA, are likely to provide insights into the drastically different forms of MRSA infection. More immediately, we need

high-quality clinical trials to inform the treatment of individuals infected with MRSA today.

The persistently high mortality associated with invasive MRSA infection — despite the fact that multiple antibiotics with effectiveness against MRSA have been approved by the FDA since 2014 — highlights the need for high-quality trials to determine optimal management

for these patients. Such studies will fall upon the clinical community to conduct and will likely require the creation of a clinical trials network to complete. Only by advancing both areas of research will we ultimately reduce the clinical impact of this persistent pathogen.

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Author contributions

The authors contributed equally to all aspects of the article.

Competing interests

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