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Review

# Methicillin-resistant *Staphylococcus aureus* is raising global concern as it overcomes immune challenges through various virulence mechanisms

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## SUMMARY

Methicillin-resistant *Staphylococcus aureus* (MRSA) in the 21st century remains a global concern with increasing rates of morbidity and mortality in healthcare settings. Hospital-associated MRSA strains have developed multidrug resistance (MDR), limiting the effectiveness of several commonly used antibiotics. First-line treatment for MRSA depends on the type of infection caused. Antibiotics such as vancomycin, linezolid, and daptomycin remain central to managing serious MRSA infections. However, the rise of MDR and the need to prevent further antibiotic resistance have led to the use of combinational antibiotic regimens to manage serious infections. Furthermore, MRSA can acquire virulence determinants and resistance plasmids via mobile genetic elements (MGEs) and stably inherit diverse resistance mechanisms, fostering hypervirulent MDR lineages that complicate clinical management. Together, these factors enable MRSA to evade host immune defences and cause serious infections with poor clinical outcomes. Collectively, this review highlights the epidemiological burden of MRSA with a better understanding of its resistance and virulence mechanisms and reinforces the need for optimized approaches to prevent, manage, and control infections.

## INTRODUCTION

A difficult-to-manage opportunistic Gram-positive bacterium, *Staphylococcus aureus,* can cause severe nosocomial infections with increased morbidity and mortality rates when it acquires resistance to β-lactam antibiotics. MRSA was initially identified in 1961 when methicillin, a narrow-spectrum β-lactam antibiotic, was used to treat *S. aureus* infections.[1] However, because of its harmful effects on humans, the antibiotic is no longer used and is mostly substituted by other penicillin family of antibiotics, such as dicloxacillin, flucloxacillin, and oxacillin. But the term "MRSA" is still in use. Furthermore, by the 1990s, the management of MRSA infections had become monotonous in hospital settings, with alarming numbers of necrotizing infections in healthy communities, which led to the infections being referred to as either healthcare-associated community-onset MRSA (HAOC-MRSA) or community-acquired MRSA (CA-MRSA).[2,3] Today, MRSA infections cause an average of $3 billion in medical expenses each year, with over 12,000 deaths reported worldwide from methicillin resistance alone.[4,5] Although a considerable number of MRSA infections in the US have been decreasing, the widespread use of injectable drugs combined with homelessness and substandard living circumstances might make our present efforts to stop the spread of infections considerably more difficult.[6]

MRSA can harbor a large array of virulence factors that are liable for colonizing, invading, and suppressing host immune

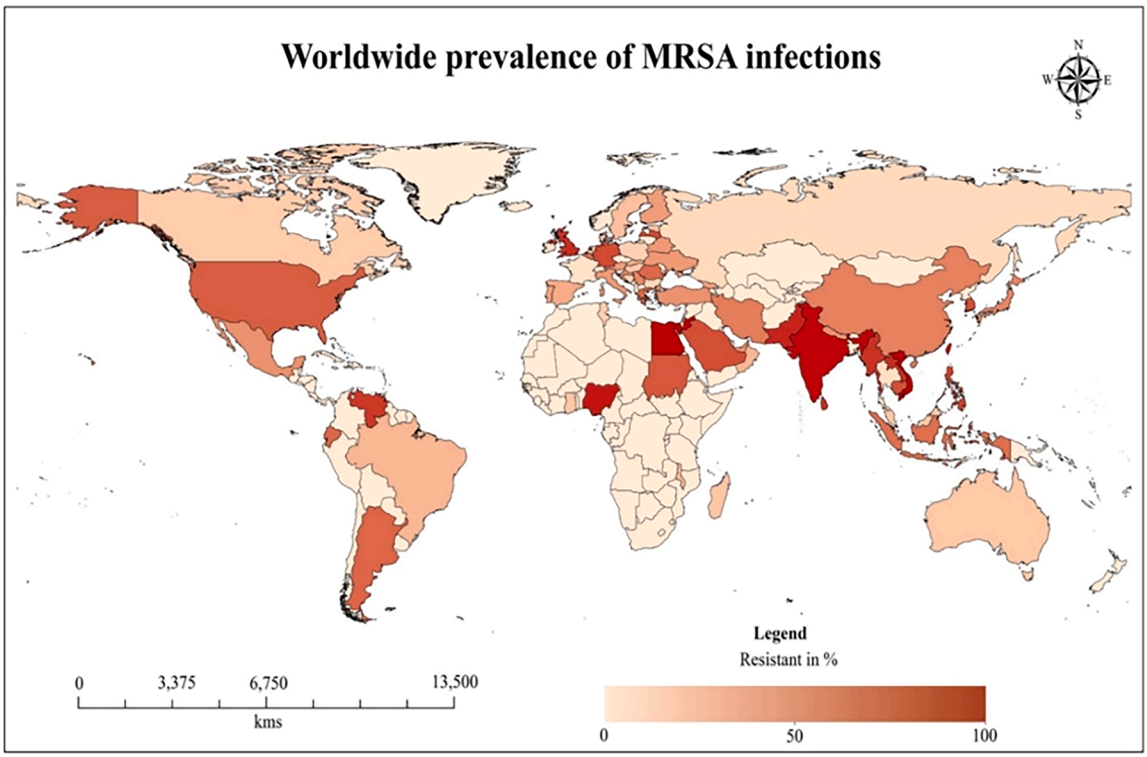


**Figure 1. Country-level choropleth map showing the estimated proportion of methicillin-resistant *Staphylococcus aureus* (MRSA) among clinical *S. aureus* infections**

The color gradient (light to dark red) represents per cent resistance from 0 to 100% (legend at bottom); darker shades indicate higher MRSA prevalence. Countries with no available estimates are left unshaded/pale. Values reflect aggregated national estimates from surveillance reports and published studies; the specific time frame and sources are provided in the main text. Differences in sampling, case mix, and laboratory methods may affect comparability across countries. The Center for Disease Dynamics, Economics & Policy Resistance Map is the source of the data collection and statistics.

Abbreviation: MRSA, methicillin-resistant *Staphylococcus aureus*.

responses. They cause infections from mild skin infections such as pimples, impetigo, boils, cellulitis, folliculitis, furuncles, carbuncles, and abscesses to life-threatening ones such as pneumonia, osteomyelitis, and cerebral abscesses, which could result in high mortality among patients. Due to their disease severity and mortality rates, the World Health Organization (WHO) has listed them as high-priority pathogens. Over time, increasing numbers of *S. aureus* clones have developed into MRSA by harboring mobile genetic elements that confer resistance to methicillin and other β-lactam antibiotics.[7]

Despite major advancements in the field of science and technology, persistent challenges continue to hinder the management of MRSA infections. Global and One-Health genomic surveillance remains inconsistent, while rapid point-of-care platforms capable of detecting *mec* variants, heteroresistance, and virulence signatures are not yet routinely deployed.[8–10] In addition, pragmatic evidence is lacking for durable decolonization strategies, the clinical role of non-traditional therapies (such as bacteriophages and anti-virulence agents), and the best ways to translate infection-control interventions into resource-constrained and community settings. This review, therefore, aims to synthesize current understanding of MRSA pathogenesis and clinical management, while highlighting emerging therapeutic and preventive approaches needed to curb its global impact.

## WORLDWIDE EPIDEMIOLOGY OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

MRSA infections are now ubiquitous and prevail as a global concern that requires immediate attention (Figure 1). The emergence of CA-MRSA strains among non-hospitalized patients in the past two decades has significantly altered the worldwide epidemiology of healthcare-acquired MRSA (HA-MRSA). For instance, a population-based retrospective study conducted by Junnila et al.[11] in the Southwest hospitals of Finland revealed a surge in CA-MRSA infections from 13% in 2007 to 43% in 2016, while also exhibiting an increased *spa* type diversity rate from 0.86 to 0.95 among 983 MRSA isolates. The overlap of *spa* types between HA- and CA-MRSA groups has made it significantly harder to differentiate between the two, leading to delayed preventive measures in communal settings. The prevalence of *spa* type diversity among intercontinental MRSA strains is a geographical marker indicative of increased rates of human migration and travel. Since the molecular characteristics of CA-MRSA and HA-MRSA are increasingly overlapping, classifying MRSA by onset/association rather than solely CA vs. HA is increasingly useful. Therefore, a more clinically and epidemiologically meaningful framework stratifies MRSA as: HO (Hospital onset; first positive culture after hospital admission), HACO

(healthcare-associated community onset; community-onset cases with prior healthcare exposure), and CA (community-associated; community onset cases without recent healthcare risk factors).[12]

The rapid dissemination of regionally predominant MRSA strains emerging from the early 1960s made headway through hospitals located in Australia, Japan, North America, and the United Kingdom before making landfall in Scandinavian countries. Regionally predominant strains, such as the PVL-positive USA300 endemic to North America, and even successful European strains such as ST22, ST30, and ST80, remain localized within their region without showing prevalence in other countries.[13] Although USA300 remains elusive outside of the United States, a clone named USA300 Latin American variant (LV) evolved in North Columbia and disseminated in parts of Belgium, Germany, and Switzerland.[14]

Intercontinental transmission of HA-MRSA clones is evidenced by single nucleotide polymorphism (SNP) analysis of the ST5 clone after the acquisition of the Staphylococcal cassette chromosome *mec* (SCC*mec*)in an ST5 MSSA strain. Such clones evolve rapidly through dissemination between countries, as seen in the case of ST239 subgroup isolates, which began in South America and Thailand and dispersed to Europe and China, respectively. The major HA-MRSA strain ST239-III, also known as the Brazilian/Hungarian variant, was predominant in Australia and later replaced by the ST22-IV strain. ST239-III remains the predominant strain in New Zealand hospitals and several parts of Africa, such as Algeria, Ghana, Kenya, Morocco, and Tunisia. While European countries such as Denmark, Finland, Iceland, Norway, and Sweden share HA-MRSA prevalence rates of less than 5%, East Asian countries continue to show prevalence rates far exceeding 70%.[15]

The MRSA *spa* type t304/ST8 is reported to have increased outbreaks in several nursing homes in Southeast Norway from 2005 to 2011, while also occurring in the Caribbean Martinique. A similar genotype (t304/ST6) dominant in Oman caused an outbreak in Copenhagen in 2015 and was detected in both Norway and the United Arab Emirates (UAE). A study conducted by Enger et al.[16] considered these genotypes and analyzed 475 MRSA t304 strains from 2008 to 2016, demonstrating that birth countries play a crucial role. While 82.6% of the ST8 group was native to Norway, around 52.9% and 24.8% of the ST6 group originated from Iraq/Syria and other Asian countries, respectively. The MRSA ST5-II clone was initially predominant in Japan around 2011, which was soon ranked fifth in prevalence after a study conducted by Kaku et al.[17] ascertained that types ST8-IV and ST1-IV were mostly responsible for causing bloodstream infections in Japan with regional disparities, particularly among the infirm population.[18] The ST5-II clone has also been documented to be predominant in both Mexican and Portuguese hospitals. The prevalence rate of MRSA infections ranges from 3% in the Netherlands and other Nordic countries to 50% in the UK and Southern European countries, with Portugal topping with a 54.3% prevalence rate.[15]

After the acquisition of the SCC*mec* element in Romania around 1995, another Type-IV MRSA clone in Europe (CC1-MRSA IV) caused outbreaks in Irish hospitals and pediatric hospitals in Italy. The prevalence of this clone increased from 1% to 19% from the years 2011–2019 in Bavaria, Germany, and is also endemic to Ireland and North-Eastern Romania.[19] The major MRSA *spa* types distributed worldwide include t001, t003, and t041 strains and are widely disseminated in European countries such as Bosnia, Croatia, Germany, Greece, Herzegovina, Italy, Luxemburg, Poland, Serbia, and Slovenia.[20] Type-III HA-MRSA clones constitute the majority of the infections in Malaysian hospitals, while their dissemination into the general populace has increased the incidence of Type-III CA-MRSA infections. Among Asian countries such as Korea, the Philippines, Thailand, Vietnam, and regions of the People's Republic of China (Hong Kong and Taiwan), the dispersion of HA-MRSA strains has led to the evolution of Type-I-III CA-MRSA strains, with SCC*mec* Type-III clones being predominant.[21–24] Specifically in China, epidemic clones include ST59 (CC59, SCC*mec* IV/V), which predominates among CA-MRSA, and ST5 (CC5, SCC*mec* II), which remains a major HA-MRSA lineage. Further, genotypes such as ST59-t437-IV and ST5-t2460-II were among the most identified clones in the regions of China during the period 2014–2020, indicating the ongoing clonal turnover and adaptation under antibiotic and ecological pressures.[25,26] A comparative analysis of diverse MRSA outbreaks from the past two decades, along with their prevalence rates, is summarised in Table 1.

In summary, previously, owing to human mitigation, HA clones such as ST239, ST5, ST22, and ST80 have been identified in continent-wide hospital settings, with CA clones (USA300) infiltrating the community. However, a dynamic shift in HA and CA clones has been identified recently, with the USA300 clone infiltrating healthcare settings, causing diseases, while traditional HA clones are being identified in the community, making it harder to classify the strains based on HA and CA for surveillance and infection control. Similarly, various pediatric and regional epidemics have revealed a crossover of SCC*mec* types between HA and CA, highlighting the necessity to categorise strains based on HO, HACO, or CA for improved monitoring and infection prevention.

## MECHANISM OF METHICILLIN RESISTANCE IN *STAPHYLOCOCCUS AUREUS*

Strains of *S. aureus* develop resistance to antibiotics such as methicillin, amoxicillin, and penicillin, making it harder to manage in the hospital settings. Methicillin resistance has been identified even before the clinical use of penicillin.[49] Resistance to these antibiotics primarily occurs with the acquisition of SCC*mec* elements via horizontal gene transfer (HGT) that encode the *mec* genes, which are capable of altering penicillin-binding proteins (PBPs) that are essential for bacterial cell wall synthesis.[50] Acquired SCC*mec,* integrates into bacterial chromosomes, and with distinct SCC*mec* types capable of influencing resistance and virulence in sensitive strains of *S. aureus* evolve to HA-MRSA and CA-MRSA.[51] Further resistance can still be acquired through *mecA*/*mecC*-mediated PBP2a expression, β-lactamase production, and regulatory mutations affecting RNA polymerase or auxiliary factors, marking methicillin resistance in *S. aureus* to be a multifactorial process. The interplay between these determinants results in variable resistance phenotypes, highlighting that mecA transcription alone is insufficient to predict resistance

**Table 1. Comparative analysis of diverse MRSA outbreaks from the past two decades**

| Time frame | Country | Sample Size | Demographics | Sample Sources | Prevalence (%) | Reference |
|---|---|---|---|---|---|---|
| 2006 | Thailand | 619 | Hospital patients | Nasal swabs, rectal swabs, and feces | 9.2 | Jariyasethpong et al.[27] |
| 2007–2008 | India | 237 | Inpatients | Pus, sputum, urine, blood, and body fluids | 29.1 | Pai et al.[28] |
| 2008 | United States | 256 | Healthcare professionals | Nasal swabs | 6.6 | Elie-Turenne et al.[29] |
| 2010 | Germany | 20,027 | Hospital patients | Nasal swabs | 2.2 | Herrmann et al.[30] |
| 2010–2016 | South Korea | 67 | Pediatric patients | Blood and soft tissues | 29.9 | Park et al.[31] |
| 2010–2017 | Netherlands | 30, 718 | Hospital patients | Nasal swabs | 0.03–0.17 | Weterings et al.[32] |
| 2011 | Uganda | 742 | Pediatric patients | Nasal swabs | 5.7 | Kateete et al.[33] |
| 2012–2013 | India | 683 | Adult patients | Nasal swabs | 2.3 | GeorGe et al.[34] |
| 2012–2013 | Pakistan | 855 | Hospital patients | Pus, body fluid, and blood | 5.26 | Khan et al.[35] |
| 2013 | Nigeria | 300 | Health care workers | Nasal swabs | 30 | Akujobi and Ezeanya-Bakpa[36] |
| 2013–2016 | Barbados | 293 | Hospitalized and non-hospitalized patients | Blood, bone, ear, fluids, tissue, urine and wounds | 19.7 | Gittens-St Hilaire et al.[37] |
| 2014–2016 | India | 132 | Inpatients and outpatients | Pus, blood, throat swabs, body fluids, and urine | 61.4 | Preeja et al.[38] |
| 2015 | Ukraine | 128 | Hospital patients | Pus samples | 19 | Salmanov and Verner[39] |
| 2016 | Eritrea | 130 | Hospital patients | Swabs from abscess, burns, surgical wounds, and lesions | 72.0 | Garoy et al.[40] |
| 2016 | Oman | 311 | Health care workers | Nasal swabs | 15.1 | Pathare et al.[41] |
| 2017–2019 | India | 13, 506 | Hospital patients | Pus, wound, throat, ear swabs, blood, and urine | 33.7 | Sangwan et al.[42] |
| 2018 | Iraq | 109 | Hospital staff and community students | Nasal swabs | 50.4 | Hussein et al.[43] |
| 2019 | Nepal | 524 | Hospital patients | Blood, urine, and sputum | 6.5 | Dhungel et al.[44] |
| 2020 | Ethiopia | 54 | Adult patients | Midstream urine samples | 42.59 | Mitiku et al.[45] |
| 2020–2022 | Saudi Arabia | 152 | Pediatric and maternal patients | Pus, abscesses, blood, and surgical wounds. | 45.4 | Almutairi et al.[46] |
| 2021–2022 | China | – | Mixed (hospital inpatients, community) | Clinical isolates; nasal and clinical specimens (surveillance) | ~28.9% | Liu et al.[47] |
| 2022–2024 | China | Cohort sizes vary | Hospitalized COVID-19 patients with secondary infections | Respiratory specimens/ blood | MRSA identified among bacterial co-infections; study characterizes isolates 2022–2024 | Gu et al.[48] |

levels. Proteins such as PrsA and regulatory systems such as blaR1-blaI, modulate PBP2a activity and β-lactamase expression, creating a complex regulatory network.

## Structure, origin, and resistance mechanisms of staphylococcal cassette chromosome mec and associated systems

Structurally, SCC*mec* integrates three major components: a *mec* complex carrying *mec* homologues (*mec*A/*mec*B/*mec*C/*mec*D) and their regulatory genes (*mec*R1 and *mec*I), cassette chromosome recombinase (*ccr*) complexes (*ccr*A/*ccr*B/*ccr*C), and joining regions (J regions)[13,52] that accommodate additional resistance and virulence factors. To date, fifteen SCC*mec* types (I–XV) have been identified, with SCC*mec* XV being the most recently reported.[53–56] Most of these types originate in *S. aureus* and have lower variability when compared to other coagulase-negative staphylococcal (CoNS) species.[57] Types I through III possess genes that promote antibiotic resistance and occur on large SCC*mec* elements found in HA-MRSA. Types IV and V have smaller elements on the SCC*mec* complex and are found in CA-MRSA strains such as USA300 and USA400. SCC*mec* Types I-IV and VIII are found in HA-MRSA strains,

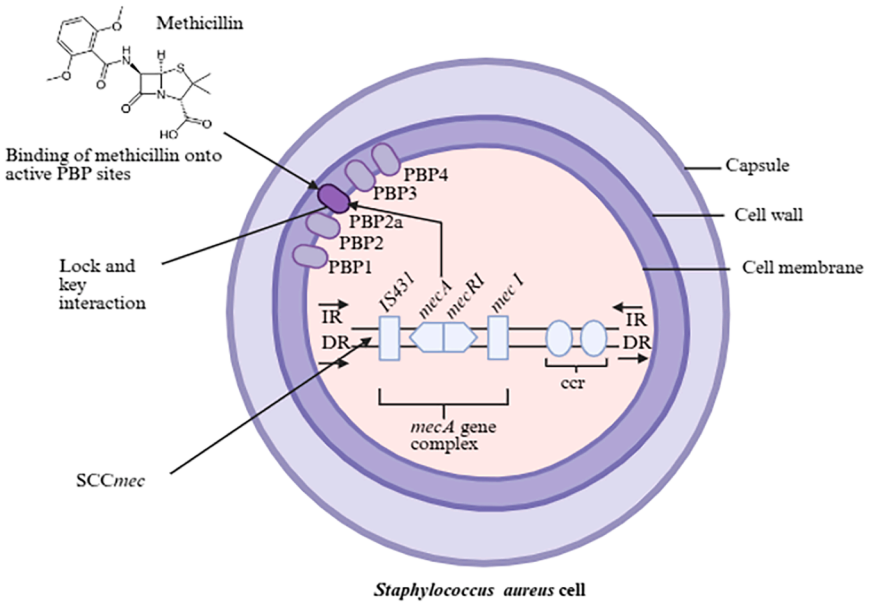


**Figure 2. An illustration of methicillin resistance conferred by PBP2a produced by the mecA gene in the SCCmec mobile element**

Methicillin (β-lactam) binds the active sites of native penicillin-binding proteins (PBPs; PBP1, PBP3, and PBP4) and inhibits transpeptidation. In MRSA, the mecA gene (within the SCCmec element) encodes PBP2a (PBP2′), a β-lactam-insensitive transpeptidase, depicted as a "lock-and-key" mismatch that allows cell-wall synthesis to continue despite methicillin exposure. The figure also outlines the mec gene complex mecA with its regulators mecI (repressor) and mecR1 (sensor–inducer), flanked by IS431 and integrated within SCCmec, which carries cassette chromosome recombinase genes (ccr) and terminal inverted/direct repeats (IR/DR) that mediate site-specific excision/integration.

whereas Types IX-XI are associated with LA-MRSA.[58] Type XI is the sole exception for containing *mec*C in place of *mec*A, which codes for PBP2a$_{LGA}$. Although fifteen SCC*mec* types are currently recognized, there remains uncertainty about the evolutionary origin of certain variants, and the mechanisms driving SCC*mec* diversification in community versus hospital strains are not fully understood.

Antibiotics aim to hijack the synthesis of various cell-sustaining components and pathways, such as the peptidoglycan cross-linked cell wall, cell membrane, synthesis of genetic material, and folic acid metabolism. β-lactam antibiotics work by inhibiting the synthesis of the *S. aureus* cell wall by binding to the four native PBPs present on the cell wall, causing the breakdown of β-lactam cyclic amides.[59] This facilitates the acylation of PBPs, which leads to the breaking down of the cell wall and inhibits MRSA proliferation. SCC*mec* encoding for *mec*A and *mec*C genes confer antibiotic resistance to most β-lactam antibiotics, including methicillin, through synthesizing PBPs that are endogenous and localized entirely within the cytoplasmic membrane (Figure 2). Recently, PBP2a$_{LGA}$, encoded by *mec*C, has low affinity for β-lactams and can cross-link peptidoglycans, sustaining cell wall synthesis despite antibiotic pressure (Figure 2).[60,61]

Additionally, J regions (J1/J2/J3) are nonessential parts of the SCC*mec* mobile element that may confer additional antibiotic resistance.[50] The subtypes of SCC*mec* elements are also classified based on the polymorphism in J regions. The J1 region carries several ORFs and regulatory genes. The J2 regions contain regulatory genes, plasmids that code for antibiotic resistance, and transposons. Transposons carry resistance genes, such as Tn554 carrying *erm*A and *spc* genes, which encode for erythromycin and mycin resistance, respectively. The J3 region includes plasmid-encoded antibiotic resistance genes such as the plasmid pUB110 encoding for bleomycin, kanamycin, and tobramycin resistance.[62,63]

## Resistance mechanisms of *mec* homologues and penicillin-binding proteins

Methicillin resistance is primarily attributed to the acquisition of the *mec* gene complex, which encodes altered PBPs with reduced affinity for β-lactams. Recent studies have documented numerous homologues of the *mec* gene, the majority of which are capable of causing increased resistance. It is therefore essential to understand these variations to effectively develop any therapeutic strategies to curtail MRSA infections. The *mec* homologues are classified according to their nucleotide sequence similarity. For instance, genes with ≥70% nucleotide similarity are classed as different *mec* types, while variations with <95% identity to a prototype are designated allotypes (e.g., *mec*A1 and *mec*A2).[64] Therefore, identifying variations in *mec* homologues is crucial to identifying resistant determinants, making it easier to predict resistance and identify any evolutionary diversification. However, there is a significant knowledge gap that needs to be addressed as sequence variants among different allotypes remain poorly determined.

### *mecA: The canonical resistance determinant*

The *mecA* gene is a part of the SCC*mec* mobile genetic element that confers resistance against β-lactam antibiotics. On exposure to β-lactam antibiotics, the transpeptidase domain of all native PBPs is inactivated. However, MRSA expressing the *mecA* gene encodes PBP2a, a PBP with low affinity for β-lactam antibiotics that allows peptidoglycan cross-linking to proceed, maintaining the integrity of cell walls, thereby rendering antibiotic resistance. Additional regulatory activation of *mecA* genes on exposure to β-lactam antibiotics has been reported in CA-MRSA strains through the regulation of *blaI* and *blaRI* genes, which are normally known to control β-lactamase activity.[65,66] Although significant progress has been made in understanding resistance mechanisms through *mecA* genes, research indicates that the overall picture is more complex, including interactions with native PBPs and various stress responses.

### mecC: A divergent homologue of mecA

The *mec*C has about 70% nucleotide identity with the *mecA* genes, and the PBPs that it encodes are PBP2a$_{LGA}$, which exhibits a higher relative affinity for oxacillin compared to PBP2a.[67–69] Notably, *mecC*-positive MRSA isolates frequently have novel SCCmec XI elements, which differ from those seen in *mecA*-positive isolates. As a result, it is possible to misdiagnose methicillin-susceptible *S. aureus* (MSSA) if laboratory tests are not sufficiently specific when *mecC* is present. However, the epidemiology of *mecC* and its contribution to human infections is still an active field of study.[70]

### β-lactamase-mediated resistance

In addition to resistance mechanisms caused by PBP2a encoded by *mecA,* MRSA strains also produce enzymes such as β-lactamases that are capable of hydrolyzing the β-lactam ring, rendering antibiotics ineffective. The 846 bp *blaZ* gene encodes a β-lactamase, and its expression is regulated by the BlaR1-BlaI system that is clustered together either in a plasmid or on the chromosome.[71] Cross-regulation between *mec*A and *bla*Z has been observed, indicating a synergistic effect in resistance.[72] However, the quantitative contribution of β-lactamases to mec-dependent resistance across different strains remains poorly defined.

### Mutations in transcriptional and translational machinery

Mutations in genes encoding RNA polymerase subunits, such as *rpoB* and *rpoC,* can alter global transcriptional responses to β-lactam stress.[72] Additionally, the chaperone-foldase PrsA influences PBP2a folding and stability, enhancing its function independently of mecA transcription.[73] Stress responses, such as the mupirocin-induced stringent response, can also potentiate PBP2a activity.[74] Further, the loss of mutation of Cyclic-di-AMP phosphodiesterase (GdpP) an enzyme that cleaves the second messenger of cyclic-di-AMP that helps in maintaining bacterial cell size, leads to increased resistance to β-lactam antibiotics.[75] Similarly, the inactivation of *cplX* or *clpP* (ATP-dependent unfoldase) reduces susceptibility to β-lactam antibiotics.[76] Serine/threonine kinase encoded cognate phosphatase (*Stp1*) in *S. aureus* plays a crucial role in cell division and morphogenesis, and its loss could cause cell wall defects. Studies introducing loss-of-function point mutation in *Stp1* have facilitated β-lactam resistance in laboratory strains that lacked both *mec*A and *bla*Z.[77] Further mutational studies in cell division genes (*ftsH*, *ftsZ*), and cell wall homeostasis (*dltA, dltA, gdpP, pbp4* promoter) of laboratory strains of *S. aureus* strains increased β-lactam resistance, which underscores that methicillin resistance in *S. aureus* is not solely dependent on the expression of *mecA* or production of β-Lactamase, but is an outcome of a complex network of auxiliary factors.[66] Hence, understanding these non-classical resistant determinants is therapeutically relevant, suggesting that existing diagnostic and treatment approaches for β-lactam-resistant *S. aureus* infections may need to be reconsidered.

### Resistance mechanisms of cassette chromosome recombinase complexes and accessory gene regulator systems

The *ccr* genes and surrounding open reading frames (ORFs) constitute the *ccr* gene complex. These complexes (*ccr*A/*ccr*B/*ccr*C) encode large serine recombinases (LSRs) that facilitate the excision and insertion of SCC*mec* in the bacterial genome and confer mobility of the chromosomal SCC*mec* ranging from 20 kb to 60 kb.[60] Similar to the nomenclature of *mec* homologues, *ccr* complexes are divided into allotypes based on nucleotide similarities. Many different genes are involved in regulating methicillin resistance. The auxiliary gene *fem* (factor essential for methicillin resistance) gene clusters help in the biosynthesis of peptidoglycan, necessary for forming the cell wall, and come in six different types (*fem*A, *fem*B, *fem*C, *fem*D, *fem*E, and *fem*F). Mutation of these genes has been shown to progressively reduce resistance to β-lactam antibiotics. Auxiliary factors such as *aux*A and *aux*B increase the expression of methicillin resistance by stabilizing lipid cells in the peptidoglycan cell wall layers.[78] The accessory gene regulator (*agr*) comes in four different groups and presents itself as a quorum sensing operon that oversees virulence factors and miscellaneous gene functions. The quorum sensing also allows it to detect the concentration of signal molecules and thereby sense the population density of its own self, allowing for gene expression. A mutation of these genes leads to the breakdown of their functioning, which significantly reduces staphylococcal virulence.[79,80] HA-MRSA strains show a high expression of *mec*A, with the caveat of lower *agr* expression in contrast to CA-MRSA strains, which exhibit lower PBP2 production but higher *agr* expression. *Agr* regulation systems are common in CA-MRSA strains such as USA300, which enhances the potential to cause invasive infections in healthy populations. Further, SCC*mec* encodes phenol-soluble modulins (PSM*mec*), which can repress *agr* in HA-MRSA strains, promoting adhesin production and increasing the risk of nosocomial infections.[81] In contrast to auxiliary factors, potentiators (*pot*) factors show an increased level of β-lactam and methicillin resistance when genetic mutations occur in them. Methicillin resistance can additionally occur in two other ways, either through the overproduction of β-lactamase or by the spontaneous mutation of PBP genes that support methicillin resistance.[82] However, the mec-agr interplay and auxiliary factor regulation are incompletely mapped. Understanding environmental and host influences on these interactions is critical for therapeutic targeting.

## VIRULENCE FACTORS INVOLVED IN THE PATHOGENESIS OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

MRSA is one of the most widespread contemporary pathogens that expresses multiple virulence factors to evade host immune responses. Membrane-damaging toxins and peptides are crucial components for its pathogenicity. Research on MRSA-MGEs at the genomic level has illustrated the intricacy of MRSA evolution, showing how specific the prevalence of MGE, gain, and loss across time is likely to be controlled by selective pressures that are weighed against fitness cost.[83] While the infections caused by MSSA and MRSA employ the same repertoire of virulence factors to cause disease, the key difference in virulence lies in the quantity and combination of virulence factors produced by different individual strains due to SCC*mec* element acquisition rather than being directly reliant on

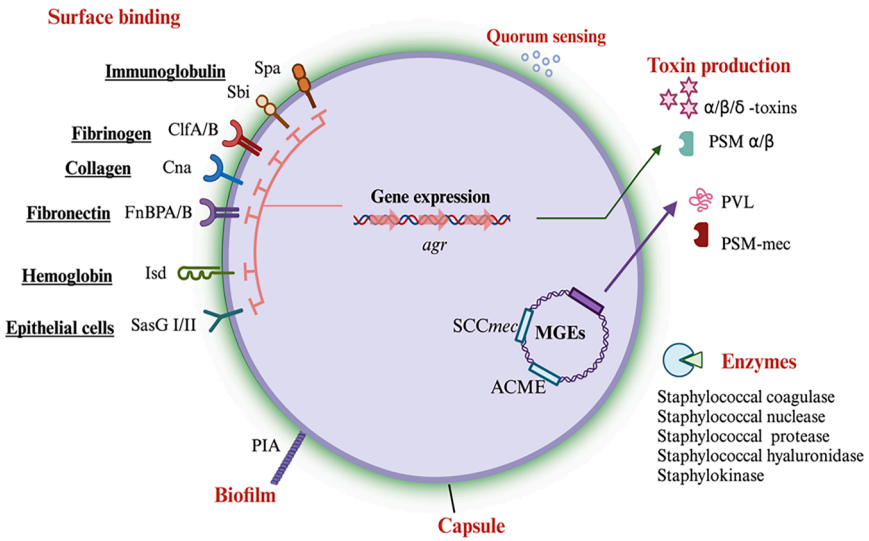


**Figure 3. Virulence factors in MRSA.**

***S. aureus* pathogenicity is mediated by multiple factors, including surface adhesins (Spa, ClfA/B, Cna, FnBPA/B, Isd, and SasG) that bind host components, and polysaccharide intercellular adhesin (PIA) for biofilm formation**

The *agr* quorum-sensing system regulates the expression of toxins (α/β/δ-toxins, PSM α, PSM-mec, and PVL) and enzymes (coagulase, nuclease, proteases, hyaluronidase, and staphylokinase). Mobile genetic elements (SCCmec, ACME) contribute to antibiotic resistance and virulence. The capsule enhances immune evasion by inhibiting phagocytosis. These secreted virulence factors help MRSA strains to breach host immune responses or help to enter host cells. These factors are either integral parts of chromosomes or are acquired through MGEs.

methicillin resistance or susceptibility. Isogenic strains of MSSA and MRSA, which only differ in the *mec*A gene, show similar levels of virulence, while successful MRSA clones such as US300 show more virulence relative to MSSA strains in general. This is because the USA300 CA-MRSA strain carries a smaller and more versatile SCC*mec* type IV/V cassette, which imposes less of a fitness cost, allowing CA-MRSA strains to focus their metabolic resources on the production of virulence factors while fully retaining their methicillin resistance, making these strains more virulent than MSSA and HO-MRSA strains.[84] Virulence factors such as PVLs are known to cause recurrent skin abscesses and necrotizing pneumonia and are rarely associated with MSSA pathogenesis, while they are consistently produced in MRSA infections. MSSA strains have a dysfunctional *agr* system leading to a weaker production of α-toxins, while MRSA strains have a highly functional regulatory *agr* system that produces high levels of α-toxins consistently, increasing their virulence. Further, as compared to HO-MRSA strains, CA-MRSA produces a higher level of PSMs in clones such as USA300 that results in its epidemic success.[85]

A distinctive factor that determines the difference in virulence between HO-MRSA strains and CA-MRSA strains is the acquisition of the SCC*mec* element and its associated fitness cost. For instance, HO-MRSA strains typically carry larger SCC*mec* types (I–III), which often harbor multiple resistance genes nonspecific to β-lactam resistance in addition to *mec*A, while CA-MRSA strains carry smaller SCCmec types (IV–V), which only contain the *mec*A gene and other necessary regulatory genes. As a result, HO-MRSA with larger SCC*mec* types undergo a fitness challenge with a significant metabolic burden, making them thrive in hospital settings where antibiotic pressure is consistent. Conversely, CA-MRSA can replicate to the same degree as MSSA and can easily thrive in communities of healthy people where there is less antibiotic pressure due to the allocation of metabolic resources for the production and expression of virulence factors and their respective genes. HO-MRSA strains suffer from a trade-off where methicillin resistance comes at a price, wherein the complete expression of virulence is sacrificed due to metabolic resources being used for replicating genes unnecessary for the production of virulence factors such as PVLs and PSMs. Smaller SCCmec cassettes allow for CA-MRSA strains to fully dedicate their metabolic resources toward the expression of virulence factors, leading to a robust *agr* quorum-sensing system and a higher degree of α-toxin production without suffering the drawbacks of acquiring methicillin resistance, unlike HO-MRSA. Smaller SCCmec cassettes are also more versatile and successful in inserting themselves into highly virulent strains such as US300.[86] In the case of US300, which possesses an SCC*mec* IV element, the acquisition of this resistance cassette is linked with the integration of a phage-encoded plasmid carrying genes for the expression of PVL toxins, thus showing that the acquisition of smaller SCC*mec* elements also gives room for acquiring genes responsible for coding major virulence factors.[85,87,88] There have been reports of several toxins that are active against the human host in a variety of MGEs found within the MRSA genome, such as exfoliative toxins, adhesins, and haemolysins. Bacteriocins are additional MGE-transferrable toxins that MRSA may use to kill rival or commensal bacteria.[89] Superantigens, lipoproteins, proteases, leukocidins, hyaluronidases, and β-type phenol-soluble modulin (PSM) genes are a few examples from a wide range of the virulence factors carried by genomic islands[89,90] (Figure 3).

## Toxins

### *Hemolysins*

The α-hemolysin is a predominantly known virulence mechanism in *S. aureus* (Figure 3). The homoheptamer of α-hemolysin monomers forms a pre-pore after attaching to the cell surface, thereby subsequently developing into a stable membrane-spanning pore. The genes that code for α-hemolysin (*hla*) are found in samples of both MRSA and MSSA strains.[91] In addition to α-hemolysin, *S. aureus* also has several additional PFTs (small β-barrel pore-forming cytotoxins). These PFTs, unlike α-hemolysin, require two polypeptides that have been given

the names S (slow) and F (fast) based on their electrophoretic mobility to create a mature pore.[92] In contrast, the β-hemolysin produced by MRSA is a neutral sphingomyelinase that hydrolyses sphingomyelin, a lipid found in plasma membranes, rather than creating pores in the cell membrane. The hemolytic activity of β-hemolysin depends on its enzymatic activity.[93,94] Further, membrane-damaging peptides, such as δ-hemolysin, are 26 amino acid (AA) short amphipathic peptides with an α-helix structure that have both hydrophobic and hydrophilic sides. δ-hemolysin could attach to the cell surface and aggregate to generate transmembrane holes, bind to the cell surface, and affect the membrane curvature, thereby disrupting the plasma membrane, or act as a deterrent to solubilize the membrane at high concentrations.[95] This family of small cytotoxic amphipathic peptides has recently expanded with the discovery of novel peptides known as PSM, initially in *S. epidermidis* and then in *S. aureus*.[96,97] MRSA strains have been identified to produce seven PSMs: PSM α1-4, PSM β1 and 2, and δ -δ-toxin hemolysin that could bind to FPR2 and trigger neutrophils.[97] Certain MRSA strains include SCC*mec* elements that encode another PSM called PSM-*mec*. PVL is a virulence factor that contributes to the severity of MRSA infections and is associated with poor outcomes. PVL is a pore-forming toxin that destroys white blood cells and alters the immune system. It is generally considered a feature of community-associated MRSA and is found integral to MGEs (Figure 3).

#### *Leukocidins*

By destroying leukocytes, leukocidins are hypothesized to protect *S. aureus* from being destroyed by host phagocytes. Leukocidins are thought to primarily target phagocytes among leukocytes.[98] Leukocidins can also affect dendritic cells, T lymphocytes, and natural killer cells, suggesting that they can impair both innate and adaptive immune responses. Some leukocidins can also lyse erythrocytes in addition to their leukocidal activity.[99] The leukocidins most likely evolved through gene duplication and shared ancestry.[98]

#### *Exfoliative toxins*

ETs are serine proteases that exhibit exquisite substrate specificity. They can hydrolyze a single peptide bond after recognition in the extracellular segment of desmoglein 1 (Dsg1). Dsg1 is a desmosomal cadherin-type cell-cell adhesion molecule. In both human and animal skin, this hydrolysis separates keratinocytes, which is crucial for staphylococcal skin infections.[100] Three different ET serotypes (ETA, ETB, and ETD) that have been linked to staphylococcal skin infections in humans, such as staphylococcal scalded skin syndrome and bullous impetigo, have been discovered in *S. aureus* to date.[101] The fact that exfoliation brought on by ETs has been reported in numerous phylogenetically remote hosts, though with varying degrees of vulnerability, suggests host specificity.[102] It has been further found that ETA, ETB, and ETD proteins are MGE-borne and are transported by a temperate phage, megaplasmid, and *S. aureus* pathogenicity islands (SaPI), respectively.[103–105]

#### *Staphylococcal enterotoxins*

*S. aureus* produces a vast array of emetic exotoxins named SEs, which cause staphylococcal food poisoning (SFP) along with other chronic conditions. Genes that code for emetic proteins are classified as "SE," while other genes suspected to exhibit emetic activity are classified as "staphylococcal enterotoxin-like" (SEIs). The gene termed "toxic shock syndrome toxin-1" (TSST-1) is proximally related to the SE family and has been correlated with fatal incidences of menstruation-associated and non-menstruation-associated toxic shock syndrome (TSS). Dicks et al., (2021) analyzed a historical repository of *S. aureus* strains belonging to the national collection of type cultures (NCTCs) containing 133 long-read sequenced strains obtained between 1924 and 2016 and around 11,000 ReqSeq genomes to identify staphylococcal enterotoxin-like (SEl) genes responsible for SE production. An analysis of seven variant genes (SEIz, SEI26, SEI27, SEI28, SEI29p, SEI30, and SES-2p) led to the discovery of five new SEI gene family members (SEI29p, SEI30, SEI31, SEI32, and SEI33).[106] The current literature describes 29 SE and SEI genes in total, with SEA-E being the five classical SE types confirmed to exhibit emetic activity and known to cause SFP. In addition to the five classical SEs, there are 24 SEI types ranging from SEG-SEIZ, SEI01, SE02, SEI26, and SEI27, which are either confirmed to display emetic activity or suspected to play a role in SFP. The SEF gene, also known as the staphylococcal pyrogenic exotoxin C (PEC) gene, is not included in this nomenclature as it was initially identified to code for the protein produced by the TSST-1 gene. This conflict in naming was resolved by simply referring to it as the "TSST-1" gene, adding to a total of 30 SE/SEI genes coding for their respective SE proteins. SEs and TSST-1 are well-studied proteins and are regarded as superantigens (SAgs) due to their capacity to bind to class II MHC molecules on antigen-presenting cells and activate T cells. *S. aureus* strains on average possess 2–18 of the SE genes described above, and a Zn-binding site of these enterotoxins is known to interact with class II MHC molecules.[107,108] The intense T cell activation results in a cytokine bolus that causes acute toxic shock. Genes encoding SEs are cardinal among mobile genetic elements.[109]

#### *Toxic shock syndrome toxin 1*

MRSA produces TSST-1, a 22-kd protein that causes staphylococcal TSS, a life-threatening condition in chronically infected patients. These toxins can interfere with major histocompatibility complex class II molecules, resulting in T cell activation and activating macrophages with enhanced cytokine production. Further, these toxins have been found to induce IFN-γ, IL-1β, IL-6, and IL-10 in human blood monocytes through LPS (lipopolysaccharide) production.[110]

### Surface-bound proteins

#### *Surface binding immunoglobulin protein*

SpA, a 40–60 kDa surface protein, is a crucial component of *S. aureus* pathogenicity and a potential vaccine candidate that efficiently prevents IgG hexamerization (Figure 3). The protein contains four or five homologous immunoglobulin (Ig)-binding domains (E, D, A, B, and C) of 56–61 residues, followed by a polymorphic variable repeat region (Xr) and a conserved region (Xc), which contains a cell-wall attachment sequence.[111] SpA interacts with the Fc region of the mammalian IgGs with various degrees of selectivity. Each of the five domains of SpA can bind to both the Fc region and Fab of IgG, thereby impairing host immune defense mechanisms to clear MRSA colonisation.[112]

Similarly, Sbi is a surface-binding immunoglobulin protein (Figure 3) that helps *S. aureus* to evade host immune defense systems by avoiding neutrophil-mediated opsonophagocytosis. Sbi proteins are known to bind to Fc regions of IgG and to complement protein C3.[113]

### *Fibrinogen-binding protein and cell-bound clumping factor*

Efb, a 15.6 kDa protein, is a secreted virulence factor that aids *S. aureus* in evading the host immune system by blocking phagocytosis. These proteins can bind to both fibrinogen and complement C3b, forming a shield-like structure, thereby preventing phagocytosis. Further, inflammatory cascades are suppressed by Efb by disrupting the TRAF3/TRAF2/cIAP1 complex.[114]

Clf, a fibrinogen-binding protein that binds to fibrinogen molecules to aid in evading host immune responses.[115] Among the Clf proteins found in MRSA, ClfA and ClfB, of which ClfA is the surface protein present at all stages of growth, bind to the C-terminus of the γ-chain of fibrinogen. ClfB binds to α and β chains of fibrinogen and is primarily detected during the early exponential phase.[116]

### *The collagen-binding protein*

During MRSA infection, Cna is essential for adhesion to the host as well as immune evasion (Figure 3). Cna is a known virulence factor in septic arthritis, where the pathophysiology of the illness is correlated with the degree of adhesion to collagen. Furthermore, Cna inhibits the customary process of complement fixation by binding to the complement protein C1q.[117]

### *The hemoglobin receptors Isd*

IsdA, IsdB, IsdC, and IsdH are the iron-sequestering, surface-anchored proteins of the Isd system (Figure 3) that are expressed through the *isd*A, *isd*B, *isd*CDEFsrtBisdG, *isd*H, and *isd*I transcriptional units. When iron levels are high, the ferric uptake repressor protein (Fur) suppresses the promoters of these transcriptional units. MRSA bacteria, with the help of their surface hemoglobin receptors such as IsdH and IsdB, destabilize the heme-binding pockets, acquire more iron, and infect hosts.[118]

### *Fibronectin binding proteins*

Common FnBPs that aid MRSA strains in binding to fibrinogen, elastin, histones, and fibronectin are IFnBPA and FnBPB. The genes encoding these proteins are *fnbA* and *fnbB,* respectively, and have been found to play a vital role in biofilm-mediated pathogenicity in MRSA. Further, the *fnb* genes are subjected to control at the transcription level by Agr and Sar global regulators.[119]

### Staphylococcus aureus *surface protein G*

In *S. aureus*, SasG mediates the first attachment to skin corneocytes. Two significant divergent SasG alleles, SasG-I and SasG-II, are present in MRSA. Compared to SasG-I, SasG-II can bind to a wider range of ligands. Additionally, SasG-II has the ability to bind to many ligands, giving MRSA a clear advantage when colonizing skin.[120]

### Other extracellular enzymes

MRSA strains can produce a wide variety of enzymes (Figure 3), such as staphylococcal coagulase, nucleases, proteases, hyaluronidase and staphylokinase, as a part of their virulence factors. Coagulase enzymes are primarily located on the chromosomes and specifically bind to prothrombin in MRSA. Whereas staphylokinases are enzymes that trigger plasminogen for breaking fibrin clots, helping bacterial propagation. Staphylococcal nuclease (DNase) may degrade both DNA and RNA substrates owing to its endo/exo-nuclease activity. Two different kinds of DNase genes have been reported in the genomes of MRSA isolates: nuc (SA0746) and nuc2 (SA1160). The primary distinction between Nuc and Nuc2 is their cell localization; Nuc2 is surface bound, whereas Nuc is an extracellular enzyme with two different isoforms, NucB and NucA. Protease enzymes also play a key role in escaping the host defense mechanism. Serine proteases, metalloproteases (aureolysin/Aur), and cysteine proteases (staphopain A and staphopain B) are found cardinal among MRSA isolates. Further, staphylococcal hyaluronidase, produced by MRSA strains, breaks down hyaluronic acid into disaccharides in the extracellular matrices and biofilms, allowing the bacterium to spread and cause infections.[116]

### Capsular polysaccharides

MRSA cell walls are surrounded by polysaccharides called CPs. MRSA isolates produce between 76 and 90% of CPs, and 11 distinct serological types have been identified (CP 1-CP11) to date. These CPs contribute to the increase in the virulence of MRSA by interfering with complement and antibody-mediated opsonization, as well as hindering phagocytosis.[121]

### Biofilm and quorum sensing

Biofilm production in MRSA is a key virulence factor that helps the bacteria to colonize chronic wounds and escape host immune responses and antimicrobial agents.[122] Neutrophil extracellular traps (NETs) are structures released by neutrophils, composed of condensed chromatin and toxic proteins, which are intended to ensnare and kill pathogens through the action of antimicrobial peptides.[123] Through biofilm production MRSA can evade innate immunity by escaping NETs, macrophage phagocytosis impairment and withstanding neutrophil-mediated phagocytic death, whereas the adaptive form of immunity is compromised through the activation of exotoxins and superantigens.[124] For instance, biofilms release higher secretions of PVL and toxins that trigger neutrophils to form NETs. However, these NETs are inactive against biofilms and may disperse a few cells from the biofilm, which may result in the metastasis of the infection.[125] Furthermore, LukAB contributes to the evasion of phagocyte-mediated killing of *S. aureus*[126]. *S. aureus* is further found to employ an *arg* involved in quorum sensing signaling that may help to regulate various virulence factors and biofilm formation during infections.[127]

## ESTABLISHMENT OF INFECTION

The ability of MRSA to enter the human host is not solely determined by host immune evasion but also by the ability of MRSA to adhere to the host. The adherence capacity is facilitated by an array of surface protein interactions designated to microbial surface components recognizing adhesive matrix molecules (MSCRAMM family). Among the MSCRAMM family, Cna, FnBPA, and FnBPB have key functions in tissue adherence. Fibronectin is bound by FnBPs on the cell surface by a tandem-β-zipper process. Following internalizations by phagocytosis or FnBPs, MRSA leaves the phagosome through

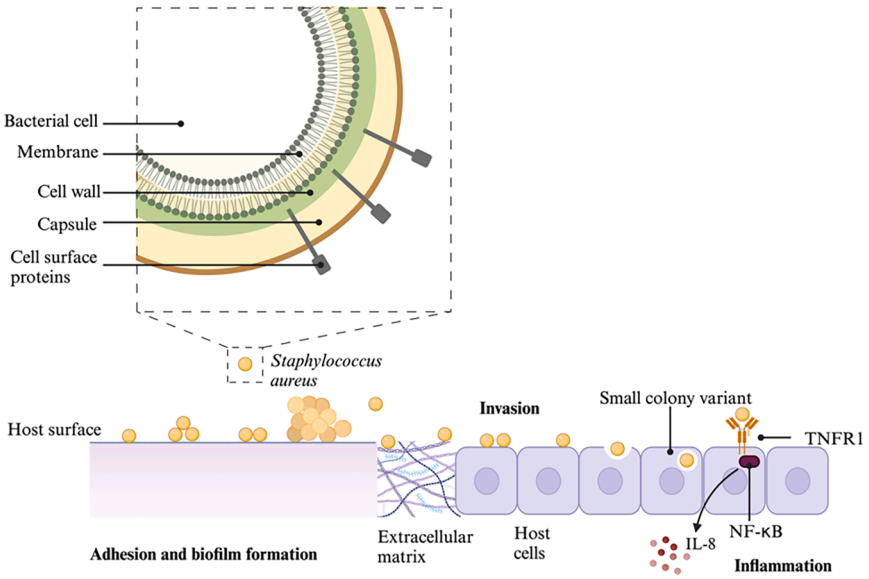


**Figure 4. Establishment of MRSA infection**

MRSA adopts various cell surface proteins to adhere to host cell surfaces. These surface proteins encourage the invasion of non-phagocytic host cells by interacting with integrins either directly or indirectly. Bacteria that live inside host cells can either induce necrosis or apoptosis, or they can go into a non-disruptive semi-dormant condition (small-colony variations). Additionally, surface proteins aid in attachment and the formation of the biofilm EPS. Host cell recognition triggers proinflammatory signaling through TNFR1, leading to NF-κB activation and interleukin-8 (IL-8) production, which promotes neutrophil recruitment and inflammation.

the PSM activity. Interactions between surface proteins on adjacent cells contribute to the accumulation phase of biofilm formation. Further, these proteins directly or indirectly interact with integrins and promote the invasion of non-phagocytic host cells. Bacteria that reside inside host cells may either cause apoptosis or necrosis, or they may enter a semi-dormant state that is non-disruptive (small-colony variants (SCVs)). Interestingly, SCVs have large levels of FnBPs, which makes it easier for nearby cells to invade when cells are lysed. Further, ClfA, ClfB, FnbpA/B, and other surface proteins assist in adhesion as well as help in the development of the biofilm EPS. It is also known that protein A of MRSA induces the production of cytokines and contributes to the pathogenesis of disease by binding to and activating tumor necrosis factor receptor 1 (TNFR1) on the epithelium of the host[128] (Figure 4).

## HOST-PATHOGEN INTERACTIONS

As our arsenal of antibiotics expands and their usage becomes more widespread, bacteria face ever-mounting challenges to survive. In response, they evolved mechanisms to resist the drugs meant to eradicate them. This tremendous modification in the microbial ecosystem has spurred scientists and healthcare professionals to investigate the intricate interaction between host and pathogen. Genomic and epidemiological investigations consistently unveil this intricate narrative, shedding light on the dynamic acquisition of MRSA and loss of host-specific adaptive genes, all orchestrated by mobile genetic elements.[129] Coexistence with the human population, typified by continuous colonization and occasional invasive infections, has supplied the crucible in which MRSA has developed a complex arsenal of mechanisms aimed at taking over the human immune system.

### Key players in immune evasion

MRSA evades host immune responses by surviving in several phagocytic and non-phagocytic host cells. One of the main causes of metastatic MRSA infections is the presence of MRSA in neutrophils, which allows the bacteria to spread throughout the bloodstream. In contrast, host invasion through non-phagocytic cells such as epithelial/endothelial cells, keratinocytes, and osteoblasts can cause chronic MRSA infections.[130] MRSA has various extracellular adherence proteins (Eap) that non-covalently inhibit neutrophil serine proteases (NSPs) at astonishingly low nanomolar concentrations.[131,132] Inhibiting NSPs serves multiple purposes and is often beneficial for the pathogen, as it helps to escape the immune surveillance triggered by the host. This also helps to surpass the neutrophilic traps.[133] Further, MRSA secretes molecules that hinder the adhesion of neutrophils to vascular endothelium, thereby resulting in the extravasation of neutrophils from blood vessels to the site of infection. Additionally, the lipases secreted by MRSA strains hinder the pro-inflammatory activity of lipoprotein pathogen-associated molecular patterns (PAMPs). The presence of capsules and hyper-biofilm-producing MRSA strains is also capable of inhibiting phagocytosis.[134]

Often, MRSA finds itself in a hostile environment inside the phagosome, where it faces yet another battle with immune cells. With the action of myeloperoxidase (MPO), the bacterium deploys peroxide ($H_2O_2$), which is toxic to the host and henceforth manipulates the immune actions triggered by the host. However, the bacterium has evolved to counter this threat by producing a specific inhibitor, aptly named the staphylococcal peroxidase inhibitor (SPIN). This inhibitor effectively binds to and inhibits MPO, providing the pathogen with an edge in evading MPO-dependent killing.[135] Further, the SPIN protein inhibits MPO, which produces the most potent ROS, hypochlorite.[136]

Lastly, NET-digesting nuclease is secreted by MRSA. α-toxin, PSMs, and bicomponent leukocidins are examples of cytolysins that directly lyse leukocytes; some of them have also been demonstrated to induce phagosomal escape or lysis upon phagocytosis in MRSA strains. Other cell types are likewise lysed by PSMs and α-toxin. Additionally, several *S. aureus* virulence factors that are released can initiate receptor-mediated apoptosis, thereby helping immune evasion and tissue damage.[134]

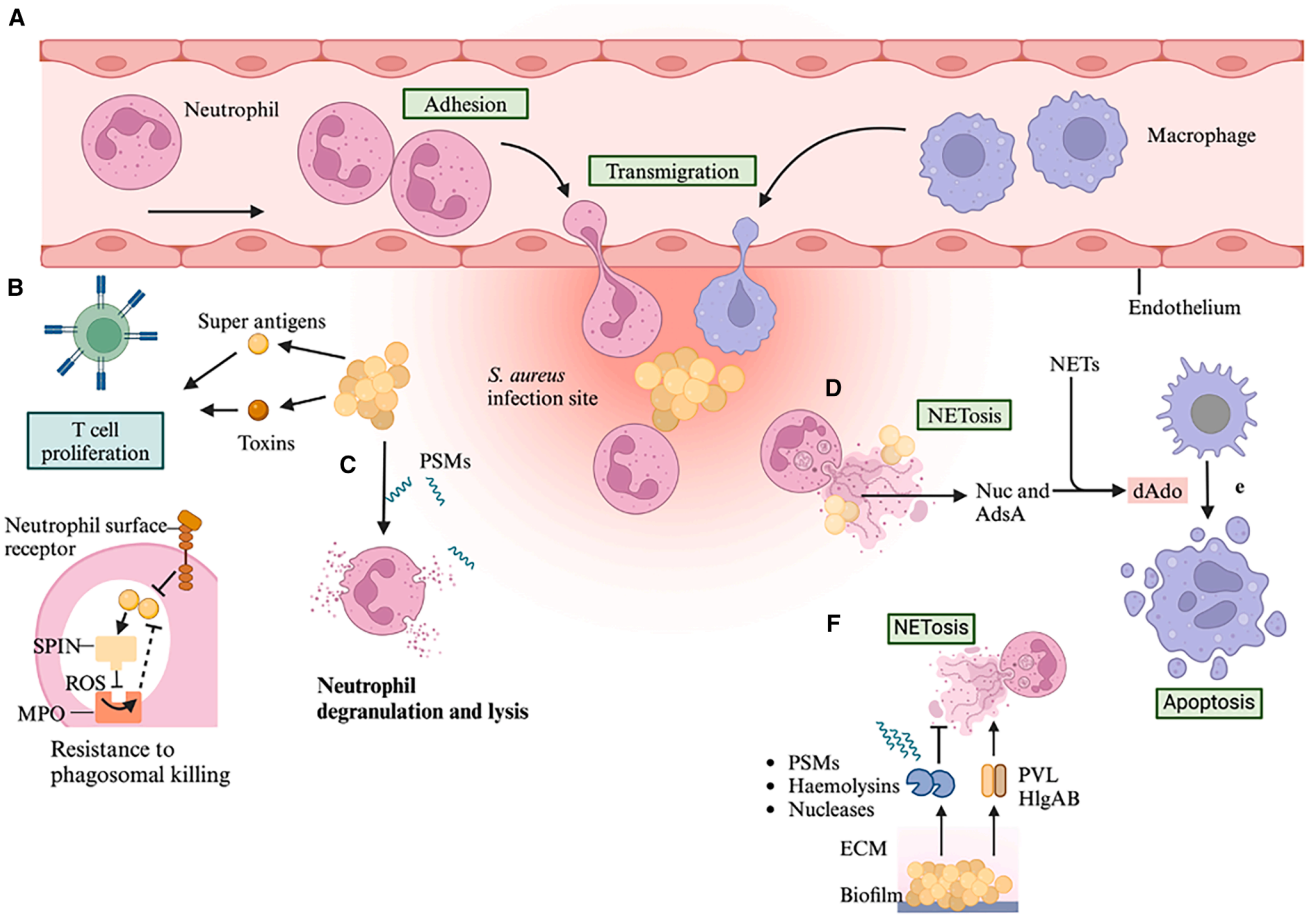


**Figure 5. MRSA host-pathogen interaction process**

(A) Neutrophils migrate to the infection site through adhesion and transmigration to respond to *S. aureus*.

(B) *S. aureus* evades the host immune response by using several factors, enabling bacterial survival.

(C) Exotoxins such as PSMs can cause neutrophil degranulation and lysis.

(D) As a response, neutrophils initiate NETosis, releasing neutrophil extracellular traps (NETs) to contain and neutralize *S. aureus*.

(E) The breakdown products of neutrophil lysis and NETs recruit macrophages to the infection site. Macrophages are triggered to engulf and remove any residual bacteria, which might result in either effective pathogen clearance or apoptosis if the bacterial burden is excessive.

(F) In cases of prolonged infection, *S. aureus* biofilm formation occurs, incorporating elements such as extracellular matrix (ECM) and persistent virulence factors (e.g., PSMs and hemolysins), which protect the bacteria and contribute to chronic infection.

## Inset description of immune evasion

The image that follows provides a graphic explanation of the MRSA infection process, showing how the bacteria cause cell death, evade immune responses, and may create persistent infections by forming biofilms. (Figure 5).

### *Initial stages of infection*

The infection begins with *S. aureus* entering host tissue and attracting neutrophils, the first responders in the immune system. The neutrophils adhere to the endothelium, migrate through the vessel wall, and move toward the infection site via chemotaxis in response to signals from the bacteria[137] (Figure 5A).

### *Neutrophil response*

Neutrophils are the first line of immune cells recruited at the site of infections caused by MRSA. However, MRSA initiates immune evasion mechanisms by producing virulence factors such as superantigens and toxins, that bind to neutrophil surface receptors. These interactions usually favor bacterial survival by inhibiting effective neutrophil recruitment, phagocytosis, and death. Additionally, these interactions enhance resistance to phagocytosis, as *S. aureus* modulates neutrophil responses by releasing proteins such as SPIN and ROS inhibitors. This allows the bacteria to survive inside neutrophils and resist degradation within phagosomes[138] (Figure 5B).

### *Neutrophil degranulation and lysis*

As neutrophils attempt to kill *S. aureus* within the phagosome, the bacteria release additional factors, including exotoxins and PSMs, which trigger neutrophil degranulation and lysis. Notably, PSMs work from within the phagosome to damage the phagosomal barrier, allowing bacteria to enter the neutrophil's cytoplasm, and at higher doses, lysis of the whole neutrophil happens. For instance, CA-MRSA (USA300), causes fast lysis of neutrophils following ingestion. This permits viable bacteria to

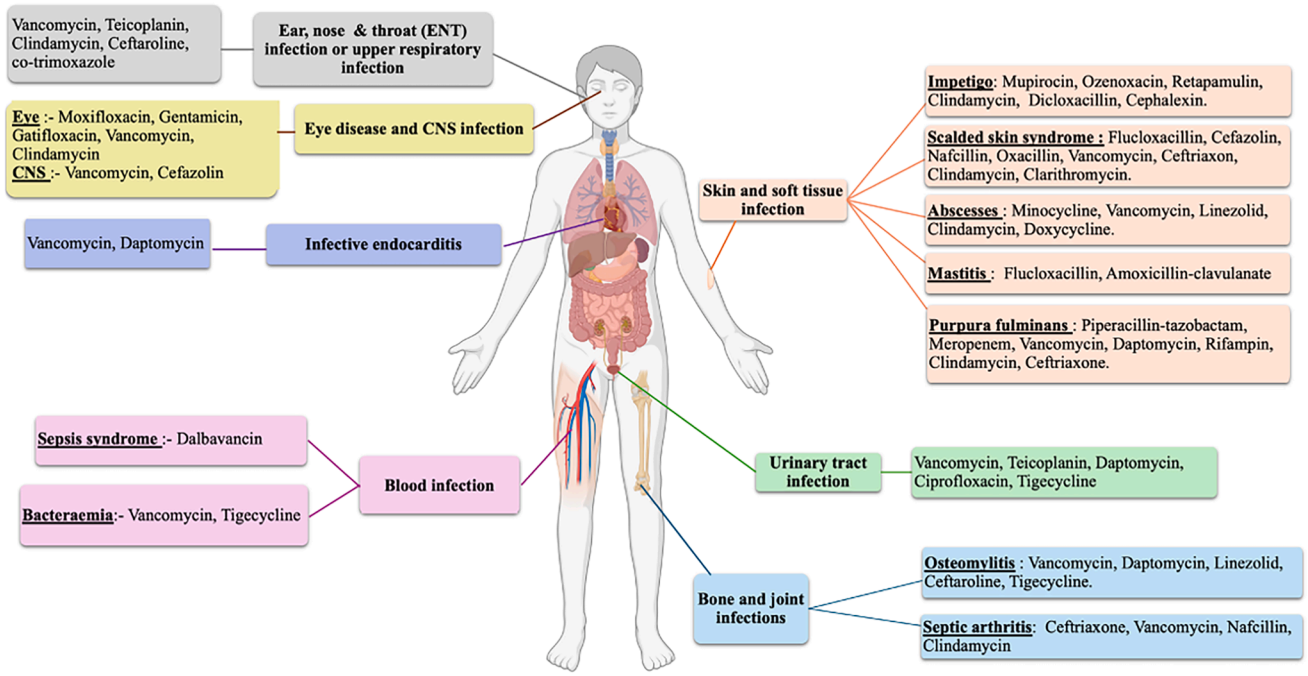


**Figure 6. Management of MRSA infections**

*S. aureus* affects multiple organ systems, causing skin, soft tissue, respiratory, ocular, CNS, bloodstream, urinary tract, and musculoskeletal infections. Recommended antimicrobial regimens vary by site and include vancomycin, daptomycin, linezolid, β-lactams, clindamycin, fluoroquinolones, tetracyclines, and topical agents.

escape from the phagosome, and perhaps the cell itself. This leads to the release of neutrophil contents, causing inflammation and local tissue damage, which can worsen infection spread[139] (Figure 5C).

### *NETosis and release of neutrophil extracellular traps*

In response to persistent infection, neutrophils undergo a special form of cell death known as NETosis. During NETosis, neutrophils release neutrophil extracellular traps (NETs) composed of DNA, antimicrobial proteins, and enzymes, which can trap and kill bacteria extracellularly. *S. aureus*, however, counters NETosis by releasing nuclease enzymes (such as Nuc and AdsA), which degrade the DNA within NETs, allowing the bacteria to escape these traps and continue their invasion[140] (Figure 5D).

### *Macrophage activation and host response*

The degradation products from neutrophil lysis and NETs attract macrophages to the infection site. Macrophages are activated to engulf and eliminate remaining bacteria, which can lead to either successful pathogen clearance or apoptosis if the bacterial burden is too high. *S. aureus* can also manipulate macrophages by inducing a form of programmed cell death, which weakens the immune defense, helping the infection to persist[141] (Figure 5E).

### *Chronic infection and biofilm formation*

In more severe infections, *S. aureus* may transition to forming biofilms, structured communities of bacteria encased in an extracellular matrix. Biofilms protect the bacteria from immune responses and antimicrobial treatments, often leading to chronic infection. The biofilm structure contains components such as ECM, PSMs, and haemolysins, making it highly resilient. This contributes to the persistent nature of some *S. aureus* infections, especially on implanted medical devices[142] (Figure 5F).

## MANAGEMENT OF METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* INFECTIONS – THE CURRENT SCENARIO

MRSA is capable of causing a wide range of infections (Figure 6), and they require careful antibiotic selection based on resistance patterns, infection severity, and patient-specific factors.

### Skin and soft tissue infections

MRSA is capable of causing a wide range of infections (Figure 6), and they are managed by a wide range of antibiotics. Some of the common skin and soft tissue infections caused by MRSA include impetigo, abscesses, scalded skin syndrome, mastitis, necrotizing fasciitis, and purpura fulminans.

### *Impetigo*

Impetigo is the most common MRSA skin infection in children aged two to five, with two main types: nonbullous and bullous.[143] The treatment involves using antibiotics such as mupirocin, retapamulin, clindamycin, ozenoxacin, and so forth.[144] Ozenoxacin has been found to show good efficacy compared to retapamulin, and during the endemic settings, oral co-trimoxazole and benzathine benzylpenicillin G injections were found to be effective further effective.[145] For localized cases, topical antibiotics such as mupirocin or retapamulin are applied for 5 to 7 days.[146] In more extensive or severe cases, oral antibiotics such as dicloxacillin, cephalexin, or clindamycin may be prescribed.

### Scalded skin syndrome

SSS causes skin denudation primarily in infants <1 year old. SSS is a rare, severe, superficial blistering skin disorder characterized by the detachment of the epidermis.[147] For treating penicillinase-resistant, anti-staphylococcal antibiotics such as flucloxacillin can be used; other options include vancomycin, ceftriaxone, clindamycin, clarithromycin (for penicillin allergy), cefazolin, nafcillin, or oxacillin.[148] Clindamycin is frequently selected as the primary treatment option because it inhibits the production of toxins and is bacteriostatic.[149]

### Abscesses

Most abscesses develop in the epiglottis or pre-epiglottic space as a result of acute supraglottitis, usually occurring due to trauma.[150] Minocycline, vancomycin, linezolid, clindamycin, and doxycycline are mostly preferred for the treatment of abscesses and are successful in reducing inflammation.[151]

### Mastitis

Inflammation of breast tissue is a common condition affecting up to 33% of lactating women. It often leads to the cessation of breastfeeding.[152] Flucloxacillin, amoxicillin-clavulanate, and dicloxacillin are the antibiotics of choice. While it helps against some bacteria, it is generally not effective against MRSA, as MRSA is resistant to penicillin. Other antibiotics are typically preferred for such infections, such as doxycycline. Diagnosing the condition through signs such as breast pain, swelling, and redness, often accompanied by fever. Pain management typically involves analgesics such as acetaminophen or ibuprofen. If symptoms are severe, appropriate antibiotics should be started, and if there is no improvement within 48 h or an abscess forms, further evaluation and drainage may be needed.[153]

### Necrotizing fasciitis

Necrotizing fasciitis is a severe, rapidly progressing soft tissue infection that destroys muscles, fat, and skin.[154] Antibiotics used are piperacillin-tazobactam, ceftriaxone, clindamycin, vancomycin, meropenem, imipenem, ciprofloxacin, daptomycin, and metronidazole (for anaerobic coverage). Prompt recognition of symptoms, such as rapid pain progression, swelling, and systemic signs such as fever, is critical. Immediate surgical consultation is essential for the aggressive debridement of necrotic tissue, as this is the cornerstone of treatment. Broad-spectrum intravenous antibiotics should be initiated as soon as possible.[155]

### Purpura fulminans

Purpura fulminans is a severe condition characterized by rapid-onset skin necrosis and the development of purplish skin lesions, often associated with disseminated intravascular coagulation (DIC). Piperacillin-tazobactam, ceftriaxone, meropenem, vancomycin, clindamycin, levofloxacin, daptomycin, and rifampin are often used in combination to treat. Management of purpura fulminans requires immediate recognition of symptoms such as sudden purpura, skin necrosis, fever, and hypotension. Supportive care includes fluid resuscitation for the hypotension and close monitoring of vital signs and oxygen levels. Broad-spectrum intravenous antibiotics should be administered promptly. Coagulation support may involve fresh frozen plasma or platelet transfusions.[156]

## Bone and joint infections

MRSA affects bones and joints, causing infections such as osteomyelitis and septic arthritis. Artificial implants in joints can shelter *S. aureus*, which forms biofilms and develops highly resistant strains. This can lead to surgical failures, multiple surgeries, and in severe cases, amputations or death.[157]

### Osteomyelitis

Osteomyelitis infection begins when MRSA bacteria invade the bone, often through wounds or nearby infections. This triggers an inflammatory response, leading to pain, swelling, and possible bone necrosis. Vancomycin, daptomycin, linezolid, ceftaroline, and tigecycline are the most preferred antibiotics. The clinical examination of osteomyelitis begins with a detailed patient history, trauma, or surgery, a neurological assessment checks for deficits that could suggest complications, and vital signs are monitored for fever or other systemic signs of infection. Imaging studies (X-rays, MRI, CT) and laboratory tests (blood cultures, inflammatory markers) are essential for confirming the diagnosis.[158]

### Septic arthritis

Septic arthritis is an infection of the joint, which leads to inflammation, swelling, and pain in the affected joint. Diagnosis starts with a detailed history to assess symptom onset, pain, and systemic signs such as fever. Joint aspiration (arthrocentesis) is performed to analyze synovial fluid for white blood cell count and culture. Supporting lab tests and imaging (such as X-rays or ultrasound) help assess the extent of the infection, and antibiotics that are found to be effective are ceftriaxone, vancomycin, nafcillin, and clindamycin.[159]

## Respiratory tract infections

Respiratory tract infections such as necrotizing pneumonia and nosocomial pneumonia, are the deadliest and are considered to be fatal among all the infections of MRSA.

### Necrotizing pneumonia

Necrotizing pneumonia is a rare and severe complication of bacterial community-acquired pneumonia (CAP). Lying on a spectrum between lung abscess and pulmonary gangrene. Commonly used antibiotics are vancomycin, linezolid, and clindamycin. However, vancomycin does not neutralize MRSA toxins, so clindamycin is sometimes added for toxin suppression. Vancomycin's lung penetration is limited but remains effective against resistant strains. Daptomycin should be avoided as it is inactivated by lung surfactant. Diagnosis includes clinical assessment, imaging, and cultures. Initial management involves broad-spectrum antibiotics and supportive care, with surgery for abscess drainage if needed.[160]

### Nosocomial pneumonia

Nosocomial pneumonia, also known as hospital-acquired pneumonia (HAP), is a lung infection that develops 48 h or more after a patient is admitted to the hospital. It is often more severe than community-acquired pneumonia. Managing nosocomial pneumonia involves quick diagnosis through symptom evaluation, imaging, and microbiological tests. Broad-spectrum antibiotics, such as piperacillin-tazobactam with vancomycin, are usually started based on local resistance patterns.[161]

## Blood infections

MRSA is primarily a cause of blood infections such as bacteremia and sepsis syndrome.

### *Bacteremia*

Bacteremia is the presence of bacteria in the bloodstream, which can lead to serious infections. Treatment typically involves intravenous antibiotics and supportive care. If left untreated, bacteremia can lead to severe complications such as sepsis or endocarditis.[162] Vancomycin is mostly preferred as a first-line antibiotic and does not use co-trimoxazole. Tigecycline can also be used as an alternative.[163] The management of bacteremia starts with confirming the diagnosis through blood cultures, ideally before antibiotic administration, while monitoring for fever and hemodynamic instability. Prompt initiation of broad-spectrum intravenous antibiotics is crucial, especially in severe cases.

### *Sepsis syndrome*

Sepsis syndrome is a life-threatening condition resulting from the body's extreme response to an infection, leading to systemic inflammation and organ dysfunction. Diagnosis is based on clinical criteria, blood cultures, and laboratory tests. Treatment typically involves prompt administration of intravenous antibiotics. Broad-spectrum intravenous antibiotics such as dalbavancin should be initiated within the first hour.[164]

## Upper respiratory tract infections

The clinical management of ear, nose, and throat (ENT) infections or upper respiratory infections involves a thorough diagnostic assessment, appropriate antibiotic therapy, and supportive care. Initially, a clinical evaluation should be conducted along with obtaining cultures from relevant sites to confirm MRSA. Empirical antibiotic therapy typically starts with broad-spectrum options such as vancomycin, teicoplanin, or daptomycin, which can be adjusted to targeted therapy based on culture results, potentially including clindamycin or ceftaroline. For minor infections, co-trimoxazole or doxycycline may be considered orally if the MRSA is susceptible. Surgical intervention may be necessary for drainage of abscesses or significant sinusitis that fails to respond to medical management.[165]

## Eye diseases and central nervous system

These infections require prompt diagnosis and tailored antibiotic therapy. For eye diseases such as conjunctivitis, keratitis, endophthalmitis, and orbital cellulitis, diagnosis involves a clinical evaluation based on symptoms such as redness, pain, and visual changes, along with cultures from ocular specimens to confirm MRSA. Treatment typically includes topical antibiotics such as moxifloxacin, gentamicin or gatifloxacin for superficial infections, while severe cases, such as endophthalmitis, may require systemic antibiotics such as vancomycin or clindamycin administered intravenously.[166] In the case of CNS infections such as meningitis or brain abscesses, diagnosis involves assessing symptoms such as fever, headache, and neurological deficits, coupled with a lumbar puncture for cerebrospinal fluid (CSF) analysis. Empirical therapy usually begins with broad-spectrum antibiotics, including vancomycin and cefazolin, until culture results are available. The treatment may be adjusted based on susceptibility patterns.[167]

## Urinary tract infections

Urinary tract infections (UTIs) are common infections that occur when bacteria enter the urinary system, affecting the bladder, urethra, or kidneys. Diagnosis typically involves urine analysis and culture to identify the causative organism. Treatment usually includes antibiotics, with choices depending on the severity of the infection and the bacterial susceptibility.[168] Antibiotics used are vancomycin, teicoplanin, daptomycin, ciprofloxacin, and tigecycline.

## Infective endocarditis

This infection occurs on the inner lining of the heart (endocardium) or heart valves, specifically caused by MRSA bacteria. Diagnosis begins with obtaining multiple sets of blood cultures to confirm the presence of MRSA, alongside echocardiography—either transthoracic or *trans*-oesophageal.[169,170] Initial treatment typically includes intravenous vancomycin, given its efficacy against MRSA, with daptomycin as an alternative for patients with renal impairment. The antibiotic therapy usually lasts 4–6 weeks, depending on the severity of the infection and the patient's response. Surgical intervention may be necessary in cases of significant valve dysfunction, persistent infection despite appropriate antibiotics, or the presence of large vegetations or abscesses.[171–173] Common antibiotics used for managing infections and their mode of action against the MRSA strain have been illustrated in Figure 7.

## Controversies, knowledge gaps, and future perspectives for methicillin-resistant *Staphylococcus aureus* management

Despite the availability of many therapies, MRSA management continues to be amid controversy owing to drug-specific limitations, evolving resistance phenotypes, and gaps in high-quality randomized data guiding some common clinical choices.[174]

### *Vancomycin: therapeutic target, efficacy limitations and "MIC creep"*

There continues to be controversy about optimal vancomycin use in serious MRSA infections: nephrotoxicity, poor tissue (specifically lung) penetration for some patients, and effects of small increases in vancomycin MICs ("Minimum Inhibitory Concentration, MIC creep") are issues. AUC-guided dosing above trough levels is the established consensus method to optimize between efficacy and toxicity, but its practice between centers varies in real-world settings.[174]

### *Contribution of toxin-suppressing adjunctive treatment (such as clindamycin or linezolid)*

Use of agents that allegedly lower toxin production (clindamycin, linezolid) in PVL-positive/necrotizing MRSA infections is based primarily on *in vitro*, animal, and observational evidence and less so on large RCTs. The value of adjunctive toxin suppression to enhance hard clinical endpoints thus remains disputed, and clinicians practice differently in the treatment of severe necrotizing pneumonia or toxin-mediated syndromes[175]

### *Biofilms, prosthetic devices, and eradication strategies*

Biofilm development on prosthetic material (joints, cardiac devices) generates high-level phenotypic resistance to antibiotics and is a predominant cause of treatment failure and reoperation. A major need is for standardized clinical approaches: antibiotic choice, best use of rifampicin combinations, suppressive therapy duration versus explanation, and adjunctive anti-biofilm techniques are all topics of current research and clinical debate.[176]

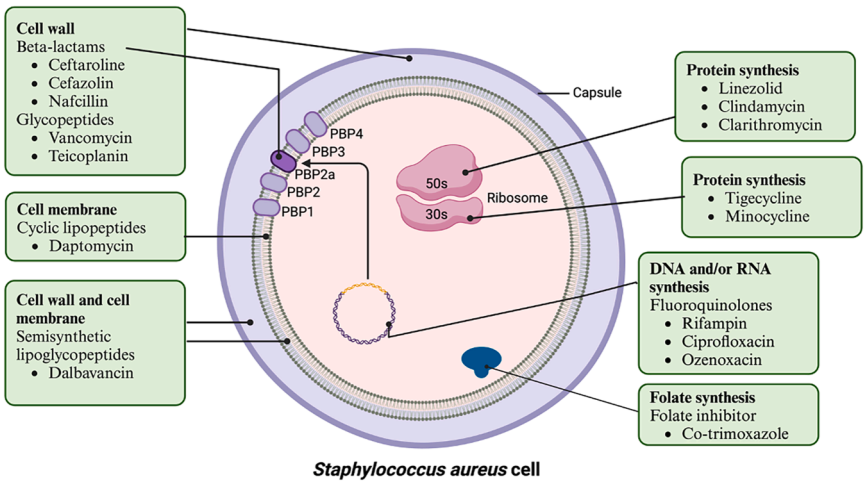


**Figure 7. Commonly used antibiotics and their mode of action against MRSA strains have been illustrated**

Cell wall synthesis (PBPs/peptidoglycan): β-lactams (e.g., cefazolin, nafcillin) inhibit transpeptidation by acylating PBPs (PBP1–4); ceftaroline retains activity against MRSA via high-affinity binding to PBP2a. Glycopeptides (vancomycin, teicoplanin) bind D-Ala–D-Ala termini, blocking transglycosylation, and transpeptidation. Cell wall and membrane: Lipoglycopeptides (dalbavancin) anchor in the membrane while binding peptidoglycan precursors, enhancing potency. Cell membrane: Daptomycin inserts into the membrane in a calcium-dependent manner, causing depolarization and rapid killing. Protein synthesis: 50S inhibitors—linezolid (oxazolidinone), clindamycin (lincosamide), clarithromycin (macrolide), block initiation or elongation; 30S inhibitors, minocycline (tetracycline), and tigecycline (glycylcycline)—prevent aminoacyl-tRNA binding. DNA/RNA synthesis: Ciprofloxacin and ozenoxacin (quinolones) inhibit DNA gyrase/topoisomerase IV; rifampin blocks RNA polymerase. Folate synthesis: Co-trimoxazole inhibits sequential steps in tetrahydrofolate synthesis. Drug lists are representative; activity varies with resistance mechanisms (e.g., mecA/PBP2a, erm-mediated MLSB resistance, tet genes, and quinolone target mutations).

### *Knowledge gaps for the newer drugs and how to place them in clinical practice*

The newer anti-MRSA drugs such as ceftaroline, tedizolid, omadacycline, eravacycline, and oritavancin, provide promising therapeutic options, but there are significant knowledge gaps about how best to use them in severe MRSA infection. Ceftaroline has been studied in MRSA pneumonia in a recent systematic review, showing some clinical effectiveness in patients with MRSA pneumonia, but a wide range of data from only case series or observational studies, not strong randomized trials.[177] Similarly, eravacycline exhibits strong *in vitro* activity against MRSA in isolates from patients with cancer, proposing potential but lacks clinical trials in invasive MRSA infections.[178] Omadacycline was evaluated in randomized controlled trials in cSSTIs, with noninferior clinical effectiveness to linezolid and similar safety profiles, but its activity in invasive MRSA infections is unproven.[179] Tedizolid, in comparison with linezolid for acute bacterial skin and skin structure infection in a meta-analysis, showed noninferiority of efficacy and slightly better toxicity profiles (fewer GI side effects, less neutropenia) in MRSA cases; but again, evidence is predominantly restricted to skin/soft tissue infection, not invasive infection.[180]

## OTHER NOVEL THERAPEUTICS TO MANAGE METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

### Nanoparticle based approaches to curb methicillin-resistant *Staphylococcus aureus*

Nanoparticles (NPs) are now a leading trend in finding a solution for antibiotic resistance. Phospholipid NPs made from penicillin G enhanced the cellular absorption of the drug and eliminated intracellular MRSA in infected A549 lung epithelial cells.[181] Recently, dialdehyde nanocrystalline cellulose NPs with increasing aldehyde group concentrations were found to have strong antibacterial activity against Gram-positive pathogens *in vitro* and to reduce the quantity of MRSA on the skin of infected mouse models.[182] Bacterial biofilms on wounds cause them to heal more slowly and stay open longer than they should. MRSA biofilm-infected wounds treated *in vivo* with nitric oxide-releasing chitosan NPs exhibited improved epithelialization, collagen deposition, decreased wound size, and rapid biofilm dispersal.[183] Further chitosan-Ag nanocomposites had a strong bactericidal effect on MRSA both *in vitro* and *in vivo.*[184] Further, Alginate-loaded NPs in conjugation with essential oils enhanced antibacterial activity against MRSA.[185] Copper-containing ferrite NPs were also reported to show excellent antibacterial activity against MRSA, with a minimum inhibitory concentration (MIC) of 1 μg/mL.[186] More significantly, MRSA cell membranes exposed to CuFe NPs experienced severe rupture and cell contents leakage. Moreover, CuFe NPs led to an excessive intracellular buildup of exogenous reactive oxygen species (ROS) and dramatically decreased the iron ions necessary for bacterial growth.[186] Recently, Hyaluronic acid-based NPs were 72 times more effective than free medicine at fighting MRSA.[187] Furthermore, MRSA is more effectively killed by gentamicin-filled gentamicin-virus-shaped mesoporous $SiO_2$-coated Silver nanocubes than by other antibiotics.[188]

### Radiation therapy

Radiation therapy, which employs powerful beam energy, photons, or other forms of energy to destroy cancer cells, is typically used to treat cancer. Radiation will enter the patient's body during brachytherapy. MRSA is efficiently killed by pulse laser therapy, which also reduces treatment duration. It is perfect for clinical applications because it does not produce any heat or pain. When the infection spreads and forms a biofilm or slimy accumulation of bacteria, which is more challenging to cure, diabetic individuals with open wounds are particularly vulnerable to MRSA.[189] Researchers at Boston University College of Engineering developed a novel radiation therapy method that can eradicate 99.9% of MRSA.[190]

## CONCLUSION

Despite advances in diagnosis and prevention strategies, MRSA continues to be a serious healthcare issue. MRSA can be difficult

to treat, particularly in patients who are at high risk of complications or have toxigenic or multidrug-resistant strains. Early detection of MRSA is a critical step toward the timely implementation of suitable treatment. New molecular and immunochromatographic testing technologies have the potential to significantly reduce diagnostic and therapy delays. Furthermore, there is an urgent need for innovative antibiotics, providing viable alternatives for strains that have developed resistance to conventional drugs. While these advancements do not eliminate the need for attention and effective MRSA prevention methods, they do help to alleviate some of the difficulties associated with MRSA management.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

## REFERENCES

1. Jevons, M.P. (1961). "Celbenin"-resistant staphylococci. Br. Med. J. *1*, 124–125.
2. Moreno, F., Crisp, C., Jorgensen, J.H., and Patterson, J.E. (1995). Methicillin-resistant Staphylococcus aureus as a community organism. Clin. Infect. Dis. *21*, 1308–1312. https://doi.org/10.1093/clinids/21.5.1308.
3. Herold, B.C., Immergluck, L.C., Maranan, M.C., Lauderdale, D.S., Gaskin, R.E., Boyle-Vavra, S., Leitch, C.D., and Daum, R.S. (1998). Community-acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. JAMA *279*, 593–598. https://doi.org/10.1001/jama.279.8.593.
4. Shoaib, M., Aqib, A.I., Muzammil, I., Majeed, N., Bhutta, Z.A., Kulyar, M.F.E.A., Fatima, M., Zaheer, C.N.F., Muneer, A., Murtaza, M., et al. (2022). MRSA compendium of epidemiology, transmission, pathophysiology, treatment, and prevention within one health framework. Front. Microbiol. *13*, 1067284. https://doi.org/10.3389/fmicb.2022.1067284.
5. Murray, C.J.L., Ikuta, K.S., Sharara, F., Swetschinski, L., Robles Aguilar, G., Gray, A., Han, C., Bisignano, C., Rao, P., Wool, E., et al. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet *399*, 629–655. https://doi.org/10.1016/S0140-6736(21)02724-0.
6. O'Neill, J. (2016). Review on antimicrobial resistance: tackling drug-resistant infections globally: final report and recommendations. https://www.cabidigitallibrary.org/doi/full/10.5555/20173071720.
7. Chambers, H.F., and DeLeo, F.R. (2009). Waves of resistance: Staphylococcus aureus in the antibiotic era. Nat. Rev. Microbiol. *7*, 629–641. https://doi.org/10.1038/nrmicro2200.
8. Karunakaran, S., Pless, L.L., Ayres, A.M., Ciccone, C., Penzelik, J., Sundermann, A.J., Martin, E.M., Griffith, M.P., Waggle, K., Hodges, J.C., et al. (2024). Impact of discontinuation of contact precautions on surveillance-and whole genome sequencing-defined methicillin-resistant Staphylococcus aureus healthcare-associated infections. Antimicrob. Steward. Healthc. Epidemiol. *4*, e97. https://doi.org/10.1017/ash.2024.89.
9. Chen, W., Zhang, J., Wei, H., Su, J., Lin, J., Liang, X., Chen, J., Zhou, R., Li, L., Lu, Z., and Sun, G. (2024). Rapid and sensitive detection of methicillin-resistant Staphylococcus aureus through the RPA-Pf Ago system. Front. Microbiol. *15*, 1422574. https://doi.org/10.3389/fmicb.2024.1422574.
10. Russell, C.D., Ke, M., Dewar, S., Gadsby, N.J., Olson, E.S., and Wootton, M. (2025). Glycopeptide Heteroresistance Among Coagulase-Negative Staphylococci: A Systematic Review and Meta-analysis. Open Forum Infect. Dis. *12*, ofaf494. https://doi.org/10.1093/ofid/ofaf494.
11. Junnila, J., Hirvioja, T., Rintala, E., Auranen, K., Rantakokko-Jalava, K., Silvola, J., Lindholm, L., Gröndahl-Yli-Hannuksela, K., Marttila, H., and Vuopio, J. (2020). Changing epidemiology of methicillin-resistant Staphylococcus aureus in a low endemicity area—new challenges for MRSA control. Eur. J. Clin. Microbiol. Infect. Dis. *39*, 2299–2307. https://doi.org/10.1007/s10096-020-03824-9.
12. Wang, S.-H., Hines, L., van Balen, J., Mediavilla, J.R., Pan, X., Hoet, A.E., Kreiswirth, B.N., Pancholi, P., and Stevenson, K.B. (2015). Molecular and clinical characteristics of hospital and community onset methicillin-resistant Staphylococcus aureus strains associated with bloodstream infections. J. Clin. Microbiol. *53*, 1599–1608. https://doi.org/10.1128/JCM.03147-14.
13. Turner, N.A., Sharma-Kuinkel, B.K., Maskarinec, S.A., Eichenberger, E.M., Shah, P.P., Carugati, M., Holland, T.L., and Fowler, V.G., Jr. (2019). Methicillin-resistant Staphylococcus aureus: an overview of basic and clinical research. Nat. Rev. Microbiol. *17*, 203–218. https://doi.org/10.1038/s41579-018-0147-4.
14. Argudín, M.A., Deplano, A., Nonhoff, C., Yin, N., Michel, C., Martiny, D., De Keersmaecker, S.C.J., and Hallin, M. (2021). Epidemiology of the Staphylococcus aureus CA-MRSA USA300 in Belgium. Eur. J. Clin. Microbiol. Infect. Dis. *40*, 2335–2347. https://doi.org/10.1007/s10096-021-04286-3.
15. Lakhundi, S., and Zhang, K. (2018). Methicillin-resistant Staphylococcus aureus: molecular characterization, evolution, and epidemiology. Clin. Microbiol. Rev. *31*, e00020-18. https://doi.org/10.1128/cmr.00020-18.
16. Enger, H., Larssen, K.W., Damås, E.S., Aamot, H.V., Blomfeldt, A., Elstrøm, P., and Ås, C.G. (2022). A tale of two STs: molecular and clinical epidemiology of MRSA t304 in Norway 2008–2016. Eur. J. Clin. Microbiol. Infect. Dis. *41*, 209–218. https://doi.org/10.1007/s10096-021-04353-9.
17. Kaku, N., Sasaki, D., Ota, K., Miyazaki, T., and Yanagihara, K. (2022). Changing molecular epidemiology and characteristics of MRSA isolated from bloodstream infections: nationwide surveillance in Japan in 2019. J. Antimicrob. Chemother. *77*, 2130–2141. https://doi.org/10.1093/jac/dkac154.
18. Mitsumoto-Kaseida, F., Morinaga, Y., Sasaki, D., Ota, K., Kaku, N., Sakamoto, K., Kosai, K., Hasegawa, H., Hayashi, J., and Yanagihara, K. (2023). The clinical characteristics and molecular epidemiology of methicillin-resistant Staphylococcus aureus (MRSA) among very elderly people in Japan. Geriatr. Gerontol. Int. *23*, 744–749. https://doi.org/10.1111/ggi.14664.
19. Earls, M.R., Steinig, E.J., Monecke, S., Samaniego Castruita, J.A., Simbeck, A., Schneider-Brachert, W., Vremeră, T., Dorneanu, O.S., Loncaric, I., Bes, M., et al. (2021). Exploring the evolution and epidemiology of European CC1-MRSA-IV: tracking a multidrug-resistant community-associated meticillin-resistant Staphylococcus aureus clone. Microb. Genom. *7*, 000601. https://doi.org/10.1099/mgen.0.000601.
20. Kevorkijan, B.K., Petrovič, Ž., Kocuvan, A., and Rupnik, M. (2019). MRSA diversity and the emergence of LA-MRSA in a large teaching hospital in Slovenia. Acta Microbiol. Immunol. Hung. *66*, 235–246. https://doi.org/10.1556/030.65.2018.052.
21. Sit, P.S., Teh, C.S.J., Idris, N., Sam, I.C., Syed Omar, S.F., Sulaiman, H., Thong, K.L., Kamarulzaman, A., and Ponnampalavanar, S. (2017). Prevalence of methicillin-resistant Staphylococcus aureus (MRSA) infection and the molecular characteristics of MRSA bacteraemia over a two-year period in a tertiary teaching hospital in Malaysia. BMC Infect. Dis. *17*, 274. https://doi.org/10.1186/s12879-017-2384-y.
22. Ko, K.S., Lee, J.Y., Suh, J.Y., Oh, W.S., Peck, K.R., Lee, N.Y., and Song, J.H. (2005). Distribution of major genotypes among methicillin-resistant Staphylococcus aureus clones in Asian countries. J. Clin. Microbiol. *43*, 421–426. https://doi.org/10.1128/JCM.43.1.421-426.2005.
23. Thai, S.N., Thu, H.V.T., Kim, L.V.T., Quynh, N.D.T., Hai, A.T.T., Thi, N.T., Minh, H.L.N., and Quang, B.T. (2019). First report on multidrug-resistant methicillin-resistant Staphylococcus aureus isolates in children admitted

to tertiary hospitals in Vietnam. Biotechnol. *29*, 1460–1469. https://doi.org/10.4014/jmb.1904.04052.

24. Lulitanond, A., Ito, T., Li, S., Han, X., Ma, X.X., Engchanil, C., Chanawong, A., Wilailuckana, C., Jiwakanon, N., and Hiramatsu, K. (2013). ST9 MRSA strains carrying a variant of type IX SCC mec identified in the Thai community. BMC Infect. Dis. *13*, 214. https://doi.org/10.1186/1471-2334-13-214.
25. Wang, B., Xu, Y., Zhao, H., Wang, X., Rao, L., Guo, Y., Yi, X., Hu, L., Chen, S., Han, L., et al. (2022). Methicillin-resistant Staphylococcus aureus in China: a multicentre longitudinal study and whole-genome sequencing. Emerg. Microbes Infect. *11*, 532–542. https://doi.org/10.1080/22221751.2022.2032373.
26. Zhan, Q., Teng, G., Chen, W., and Yu, X. (2024). High prevalence of ST5-SCC mec II-t311 clone of methicillin-resistant Staphylococcus aureus isolated from bloodstream infections in East China. BMC Microbiol. *24*, 89. https://doi.org/10.1186/s12866-024-03232-5.
27. Jariyasethpong, T., Tribuddharat, C., Dejsirilert, S., Kerdsin, A., Tishyadhigama, P., Rahule, S., Sawanpanyalert, P., Yosapol, P., and Aswapokee, N. (2010). MRSA carriage in a tertiary governmental hospital in Thailand: emphasis on prevalence and molecular epidemiology. Eur. J. Clin. Microbiol. Infect. Dis. *29*, 977–985. https://doi.org/10.1007/s10096-010-0954-7.
28. Pai, V., Rao, V.I., and Rao, S.P. (2010). Prevalence and antimicrobial susceptibility pattern of methicillin-resistant Staphylococcus aureus [MRSA] isolates at a tertiary care hospital in Mangalore, South India. J. Lab. Physicians *2*, 82–84. https://doi.org/10.4103/0974-2727.72155.
29. Elie-Turenne, M.-C., Fernandes, H., Mediavilla, J.R., Rosenthal, M., Mathema, B., Singh, A., Cohen, T.R., Pawar, K.A., Shahidi, H., Kreiswirth, B.N., and Deitch, E.A. (2010). Prevalence and characteristics of Staphylococcus aureus colonization among healthcare professionals in an urban teaching hospital. Infect. Control Hosp. Epidemiol. *31*, 574–580. https://doi.org/10.1086/652525.
30. Herrmann, M., Petit, C., Dawson, A., Biechele, J., Halfmann, A., von Müller, L., Gräber, S., Wagenpfeil, S., Klein, R., and Gärtner, B. (2013). Methicillin-resistant Staphylococcus aureus in Saarland, Germany: a statewide admission prevalence screening study. PLoS One *8*, e73876. https://doi.org/10.1371/journal.pone.0073876.
31. Park, S.G., Lee, H.S., Park, J.Y., and Lee, H. (2019). Molecular epidemiology of Staphylococcus aureus in skin and soft tissue infections and bone and joint infections in Korean children. J. Korean Med. Sci. *34*, e315. https://doi.org/10.3346/jkms.2019.34.e315.
32. Weterings, V., Veenemans, J., van Rijen, M., and Kluytmans, J. (2019). Prevalence of nasal carriage of methicillin-resistant Staphylococcus aureus in patients at hospital admission in The Netherlands, 2010–2017: an observational study. Clin. Microbiol. Infect. *25*, 1428.e1–1428.e5. https://doi.org/10.1016/j.cmi.2019.03.012.
33. Kateete, D.P., Bwanga, F., Seni, J., Mayanja, R., Kigozi, E., Mujuni, B., Ashaba, F.K., Baluku, H., Najjuka, C.F., Källander, K., et al. (2019). CA-MRSA and HA-MRSA coexist in community and hospital settings in Uganda. Antimicrob. Resist. Infect. Control *8*, 94. https://doi.org/10.1186/s13756-019-0551-1.
34. GeorGe, K., Abdulkader, J.K., Sugumar, M., and Rajagopal, G.K. (2016). Prevalence of MRSA nasal carriage in patients admitted to a tertiary care hospital in southern India. J. Clin. Diagn. Res. *10*, DC11–DC13. https://doi.org/10.7860/JCDR/2016/18259.7262.
35. Khan, R.A., Rahman, A.U., Ahmad, A., Jaseem, M., Jabbar, A., Khan, S., Iqbal, A., Ahmad, N., Wadood, A., Rahman, T.U., et al. (2014). Prevalence and antibiotic susceptibility profile of methicillin-resistant Staphylococcus aureus (MRSA) isolated from different clinical samples in district Peshawar. J Appl Environ Biol Sci *4*, 40–46.
36. Akujobi, C., and Ezeanya-Bakpa, C.C. (2013). Prevalence of methicillin-resistant Staphylococcus aureus (MRSA) among healthcare workers in a tertiary institution in Nigeria. Orient J. Med. *25*, 82–87.
37. Gittens-St Hilaire, M.V., Chase, E., and Alleyne, D. (2020). Prevalence, molecular characteristics and antimicrobial susceptibility patterns of MRSA in hospitalized and nonhospitalized patients in Barbados. New Microbes New Infect. *35*, 100659. https://doi.org/10.1016/j.nmni.2020.100659.
38. Preeja, P.P., Kumar, S.H., and Shetty, V. (2021). Prevalence and characterization of methicillin-resistant Staphylococcus aureus from community-and hospital-associated infections: a tertiary care center study. Antibiotics *10*, 197. https://doi.org/10.3390/antibiotics10020197.
39. Salmanov, A.G., and Verner, O.M. (2017). Prevalence of methicillin-resistant Staphylococcus aureus (MRSA) in Kyiv Surgical Hospital (Ukraine). Inter. jour. antoboit. and probiot. *1*, 73–83. https://doi.org/10.31405/ijap.1-2.17.05.
40. Garoy, E.Y., Gebreab, Y.B., Achila, O.O., Tekeste, D.G., Kesete, R., Ghirmay, R., Kiflay, R., and Tesfu, T. (2019). Methicillin-Resistant Staphylococcus aureus (MRSA): Prevalence and Antimicrobial Sensitivity Pattern among Patients—A Multicenter Study in Asmara, Eritrea. Can. J. Infect. Dis. Med. Microbiol. *2019*, 8321834. https://doi.org/10.1155/2019/8321834.
41. Pathare, N.A., Asogan, H., Tejani, S., Al Mahruqi, G., Al Fakhri, S., Zafarulla, R., and Pathare, A.V. (2016). Prevalence of methicillin resistant Staphylococcus aureus [MRSA] colonization or carriage among healthcare workers. J. Infect. Public Health *9*, 571–576. https://doi.org/10.1016/j.ajic.2022.06.001.
42. Sangwan, J., Mane, P., and Lathwal, S. (2021). Prevalence pattern of MRSA from a rural medical college of North India: a cause of concern. J. Family Med. Prim. Care *10*, 752–757. https://doi.org/10.4103/jfmpc.jfmpc_1527_20.
43. Hussein, N., Salih, R.S., and Rasheed, N.A. (2019). Prevalence of methicillin-resistant Staphylococcus aureus in hospitals and community in Duhok, Kurdistan region of Iraq. Int. J. Infect. *6*, e89636. https://doi.org/10.5812/iji.89636.
44. Dhungel, S., Rijal, K.R., Yadav, B., Dhungel, B., Adhikari, N., Shrestha, U.T., Adhikari, B., Banjara, M.R., and Ghimire, P. (2021). Methicillin-Resistant Staphylococcus aureus (MRSA): prevalence, antimicrobial susceptibility pattern, and detection of mec a gene among cardiac patients from a tertiary care heart center in Kathmandu, Nepal. Infect. Dis. *14*, 11786337211037355. https://doi.org/10.1177/11786337211037355.
45. Mitiku, A., Aklilu, A., Biresaw, G., and Gize, A. (2021). Prevalence and associated factors of methicillin resistance Staphylococcus aureus (MRSA) among urinary tract infection suspected patients attending at Arba Minch General Hospital, Southern Ethiopia. Infect. Drug Resist. *14*, 2133–2142. https://doi.org/10.2147/IDR.S306648.
46. Almutairi, H., Albahadel, H., Alhifany, A.A., Aldalbahi, H., Alnezary, F.S., Alqusi, I., Mobark, M.A., and Saeed Almutairi, M. (2024). Prevalence and antimicrobial susceptibility pattern of methicillin-resistant Staphylococcus aureus (MRSA) at a maternity and children hospital in Saudi Arabia: A cross-sectional study. Saudi Pharm. J. *32*, 102001. https://doi.org/10.1016/j.jsps.2024.102001.
47. Liu, L., Wang, S., Chen, Y., Xian, X., Yu, X., Li, Y., Chen, Y., Sun, G., Cheng, L., Liu, T., et al. (2025). Nasal carriage of Staphylococcus aureus in rural China: molecular epidemiology and antimicrobial susceptibility. J. Glob. Antimicrob. Resist. *45*, 41–46. https://doi.org/10.1016/j.jgar.2025.08.004.
48. Gu, F., Zhang, Y., Sun, J., Guo, W., and Han, L. (2025). The characteristics of methicillin-resistant Staphylococcus aureus co-infection in COVID-19 pneumonia. Front. Cell. Infect. Microbiol. *15*, 1560688. https://doi.org/10.3389/fcimb.2025.1560688.
49. Harkins, C.P., Pichon, B., Doumith, M., Parkhill, J., Westh, H., Tomasz, A., de Lencastre, H., Bentley, S.D., Kearns, A.M., and Holden, M.T.G. (2017). Methicillin-resistant Staphylococcus aureus emerged long before the introduction of methicillin into clinical practice. Genome Biol. *18*, 130. https://doi.org/10.1186/s13059-017-1252-9.

50. International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements IWG-SCC (2009). Classification of staphylococcal cassette chromosome mec (SCCmec): guidelines for reporting novel SCCmec elements. Antimicrob. Agents Chemother. *53*, 4961–4967. https://doi.org/10.1128/AAC.00579-09.

51. Vestergaard, M., Frees, D., and Ingmer, H. (2019). Antibiotic resistance and the MRSA problem. Microbiol. Spectr. *7*. https://doi.org/10.1128/microbiolspec.gpp3-0057-2018.

52. Bitrus, A.A., Peter, O.M., Abbas, M.A., and Goni, M.D. (2018). Staphylococcus aureus: A review of antimicrobial resistance mechanisms. Vet. Sci.: Research and Reviews *4*, 43–54. https://doi.org/10.17582/journal.vsrr/2018/4.2.43.54.

53. Baig, S., Johannesen, T.B., Overballe-Petersen, S., Larsen, J., Larsen, A.R., and Stegger, M. (2018). Novel SCCmec type XIII (9A) identified in an ST152 methicillin-resistant Staphylococcus aureus. Infect. Genet. Evol. *61*, 74–76. https://doi.org/10.1016/j.meegid.2018.03.013.

54. Uehara, Y. (2022). Current Status of Staphylococcal Cassette Chromosome mec (SCCmec). Antibiotics *11*, 86. https://doi.org/10.3390/antibiotics11010086.

55. Lee, G.Y., Lee, S.I., Seong, H.J., and Yang, S.J. (2025). Novel Variants of SCC mec Type IX Identified in Clonal Complex 398 Livestock-Associated Methicillin-Resistant Staphylococcus aureus from Pork Production Systems in Korea. Antibiotics *14*, 217. https://doi.org/10.3390/antibiotics14030217.

56. Wang, W., Hu, Y., Baker, M., Dottorini, T., Li, H., Dong, Y., Bai, Y., Fanning, S., and Li, F. (2022). Novel SCC mec type XV (7A) and two pseudo-SCC mec variants in foodborne MRSA in China. J. Antimicrob. Chemother. *77*, 903–909. https://doi.org/10.1093/jac/dkab500.

57. Wolska-Gębarzewska, M., Międzobrodzki, J., and Kosecka-Strojek, M. (2024). Current types of staphylococcal cassette chromosome mec (SCC mec) in clinically relevant coagulase-negative staphylococcal (CoNS) species. Crit. Rev. Microbiol. *50*, 1020–1036. https://doi.org/10.1080/1040841X.2023.2274841.

58. Liu, W.-T., Chen, E.Z., Yang, L., Peng, C., Wang, Q., Xu, Z., and Chen, D.Q. (2021). Emerging resistance mechanisms for 4 types of common anti-MRSA antibiotics in Staphylococcus aureus: A comprehensive review. Microb. Pathog. *156*, 104915. https://doi.org/10.1016/j.micpath.2021.104915.

59. Bush, K., and Bradford, P.A. (2016). β-Lactams and β-lactamase inhibitors: an overview. Cold Spring Harb. Perspect. Med. *6*, a025247. https://doi.org/10.1101/cshperspect.a025247.

60. Wang, H., and He, J. (2025). In Silico Exploration of Staphylococcal Cassette Chromosome mec (SCC mec) Evolution Based on Phylogenetic Relationship of ccrAB/C. Microorganisms *13*, 153. https://doi.org/10.3390/microorganisms13010153.

61. Kim, C., Milheiriço, C., Gardete, S., Holmes, M.A., Holden, M.T.G., de Lencastre, H., and Tomasz, A. (2012). Properties of a novel PBP2A protein homolog from Staphylococcus aureus strain LGA251 and its contribution to the β-lactam-resistant phenotype. J. Biol. Chem. *287*, 36854–36863. https://doi.org/10.1074/jbc.M112.395962.

62. Hou, Z., Liu, L., Wei, J., and Xu, B. (2023). Progress in the prevalence, classification and drug resistance mechanisms of methicillin-resistant Staphylococcus aureus. Infect. Drug Resist. *16*, 3271–3292. https://doi.org/10.2147/IDR.S412308.

63. Manandhar, S., Karn, D., Shrestha, M.R., Shakya, J., and Singh, A. (2025). Biofilm formation, methicillin resistance and SCC mec types among Staphylococcus aureus isolated from clinical samples from a tertiary care hospital, in Nepal. BMC Infect. Dis. *25*, 534. https://doi.org/10.1186/s12879-025-10943-1.

64. Liu, J., Chen, D., Peters, B.M., Li, L., Li, B., Xu, Z., and Shirliff, M.E. (2016). Staphylococcal chromosomal cassettes mec (SCCmec): A mobile genetic element in methicillin-resistant Staphylococcus aureus. Microb. Pathog. *101*, 56–67. https://doi.org/10.1016/j.micpath.2016.10.028.

65. Snitser, O., Russ, D., Stone, L.K., Wang, K.K., Sharir, H., Kozer, N., Cohen, G., Barr, H.M., and Kishony, R. (2020). Ubiquitous selection for mecA in community-associated MRSA across diverse chemical environments. Nat. Commun. *11*, 6038. https://doi.org/10.1038/s41467-020-19825-3.

66. Lade, H., and Kim, J.-S. (2023). Molecular determinants of β-lactam resistance in methicillin-resistant Staphylococcus aureus (MRSA): an updated review. Antibiotics *12*, 1362. https://doi.org/10.3390/antibiotics12091362.

67. Maree, M., Thi Nguyen, L.T., Ohniwa, R.L., Higashide, M., Msadek, T., and Morikawa, K. (2022). Natural transformation allows transfer of SCC mec-mediated methicillin resistance in Staphylococcus aureus biofilms. Nat. Commun. *13*, 2477. https://doi.org/10.1038/s41467-022-29877-2.

68. Watkins, R.R., Holubar, M., and David, M.Z. (2019). Antimicrobial resistance in methicillin-resistant Staphylococcus aureus to newer antimicrobial agents. Antimicrob. Agents Chemother. *63*, e01216-19. https://doi.org/10.1128/aac.01216-19.

69. Abebe, A.A., and Birhanu, A.G. (2023). Methicillin resistant Staphylococcus aureus: molecular mechanisms underlying drug resistance development and novel strategies to combat. Infect. Drug Resist. *16*, 7641–7662. https://doi.org/10.2147/IDR.S428103.

70. Abdullahi, I.N., Latorre-Fernández, J., Reuben, R.C., Trabelsi, I., González-Azcona, C., Arfaoui, A., Usman, Y., Lozano, C., Zarazaga, M., and Torres, C. (2023). Beyond the wild MRSA: genetic features and phylogenomic review of mecC-mediated methicillin resistance in non-aureus staphylococci and mammaliicocci. Microorganisms *12*, 66. https://doi.org/10.3390/microorganisms12010066.

71. Holden, M.T.G., Feil, E.J., Lindsay, J.A., Peacock, S.J., Day, N.P.J., Enright, M.C., Foster, T.J., Moore, C.E., Hurst, L., Atkin, R., et al. (2004). Complete genomes of two clinical Staphylococcus aureus strains: evidence for the rapid evolution of virulence and drug resistance. Proc. Natl. Acad. Sci. USA *101*, 9786–9791. https://doi.org/10.1073/pnas.0402521101.

72. Bilyk, B.L., Panchal, V.V., Tinajero-Trejo, M., Hobbs, J.K., and Foster, S.J. (2022). An interplay of multiple positive and negative factors governs methicillin resistance in Staphylococcus aureus. Microbiol. Mol. Biol. Rev. *86*, e0015921. https://doi.org/10.1128/mmbr.00159-21.

73. Jousselin, A., Manzano, C., Biette, A., Reed, P., Pinho, M.G., Rosato, A.E., Kelley, W.L., and Renzoni, A. (2015). The Staphylococcus aureus chaperone PrsA is a new auxiliary factor of oxacillin resistance affecting penicillin-binding protein 2A. Antimicrob. Agents Chemother. *60*, 1656–1666. https://doi.org/10.1128/AAC.02333-15.

74. Lee, A.S., de Lencastre, H., Garau, J., Kluytmans, J., Malhotra-Kumar, S., Peschel, A., and Harbarth, S. (2018). Methicillin-resistant Staphylococcus aureus. Nat. Rev. Dis. Primers *4*, 18033.

75. Argudín, M.A., Roisin, S., Nienhaus, L., Dodémont, M., de Mendonça, R., Nonhoff, C., Deplano, A., and Denis, O. (2018). Genetic diversity among Staphylococcus aureus isolates showing oxacillin and/or cefoxitin resistance not linked to the presence of mec genes. Antimicrob. Agents Chemother. *62*, e00091-18. https://doi.org/10.1128/aac.00091-18.

76. Bæk, K.T., Gründling, A., Mogensen, R.G., Thøgersen, L., Petersen, A., Paulander, W., and Frees, D. (2014). β-Lactam resistance in methicillin-resistant Staphylococcus aureus USA300 is increased by inactivation of the ClpXP protease. Antimicrob. Agents Chemother. *58*, 4593–4603. https://doi.org/10.1128/AAC.02802-14.

77. Chatterjee, A., Poon, R., and Chatterjee, S.S. (2020). Stp1 loss of function promotes β-lactam resistance in Staphylococcus aureus that is independent of classical genes. Antimicrob. Agents Chemother. *64*, e02222-19. https://doi.org/10.1128/aac.02222-19.

78. Monteiro, J.M., Covas, G., Rausch, D., Filipe, S.R., Schneider, T., Sahl, H.G., and Pinho, M.G. (2019). The pentaglycine bridges of Staphylococcus aureus peptidoglycan are essential for cell integrity. Sci. Rep. *9*, 5010. https://doi.org/10.1038/s41598-019-41461-1.

79. Fitzgerald, J.R., and Holden, M.T.G. (2016). Genomics of natural populations of Staphylococcus aureus. Annu. Rev. Microbiol. *70*, 459–478. https://doi.org/10.1146/annurev-micro-102215-095547.

80. Ali Alghamdi, B., Al-Johani, I., Al-Shamrani, J.M., Musamed Alshamrani, H., Al-Otaibi, B.G., Almazmomi, K., and Yusnoraini Yusof, N. (2023). Antimicrobial resistance in methicillin-resistant Staphylococcus aureus. Saudi J. Biol. Sci. *30*, 103604. https://doi.org/10.1016/j.sjbs.2023.103604.

81. Kawayanagi, T., Kawada-Matsuo, M., Kusaka, S., Yasutomi, Y., Suzuki, Y., Nishihama, S., Le, M.N.T., Sugawara, Y., Hisatsune, J., Kutsuno, S., et al. (2025). Clinical and genetic analysis of oral and nasal staphylococcus aureus isolates in dental patients. Sci. Rep. *15*, 13149. https://doi.org/10.1038/s41598-025-93773-0.

82. Carretto, E., Visiello, R., and Nardini, P. (2018). In Methicillin resistance in Staphylococcus aureus. Pet-To-Man Travelling Staphylococci (Elsevier), pp. 225–235. https://doi.org/10.1016/B978-0-12-813547-1.00017-0.

83. Jamrozy, D., Coll, F., Mather, A.E., Harris, S.R., Harrison, E.M., MacGowan, A., Karas, A., Elston, T., Estée Török, M., Parkhill, J., and Peacock, S.J. (2017). Evolution of mobile genetic element composition in an epidemic methicillin-resistant Staphylococcus aureus: temporal changes correlated with frequent loss and gain events. BMC Genom. *18*, 684. https://doi.org/10.1186/s12864-017-4065-z.

84. Horváth, A. (2021). Antibiotic resistance, virulence and clonal diversity of methicillin resistant and sensitive Staphylococcus aureus isolates. https://repo.lib.semmelweis.hu/bitstream/handle/123456789/9118/horv%C3%A1thandrea.e.pdf?sequence=4.

85. Thurlow, L.R., Joshi, G.S., and Richardson, A.R. (2012). Virulence strategies of the dominant USA300 lineage of community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA). FEMS Immunol. Med. Microbiol. *65*, 5–22. https://doi.org/10.1111/j.1574-695X.2012.00937.x.

86. Durhan, E., Korcan, S.E., Altindis, M., and Konuk, M. (2017). Fitness and competitive growth comparison of methicillin resistant and methicillin susceptible Staphylococcus aureus colonies. Microb. Pathog. *106*, 69–75. https://doi.org/10.1016/j.micpath.2016.06.009.

87. Otto, M. (2013). Community-associated MRSA: what makes them special? Int. J. Med. Microbiol. *303*, 324–330. https://doi.org/10.1016/j.ijmm.2013.02.007.

88. Read, T.D., Petit, R.A., III, Yin, Z., Montgomery, T., McNulty, M.C., and David, M.Z. (2017). USA300 MRSA lineages persist on multiple body sites following infectionPriprint at. bioRxiv. https://doi.org/10.1101/192096.

89. Malachowa, N., and DeLeo, F.R. (2010). Mobile genetic elements of Staphylococcus aureus. Cell. Mol. Life Sci. *67*, 3057–3071. https://doi.org/10.1007/s00018-010-0389-4.

90. Lindsay, J.A., and Holden, M.T.G. (2004). Staphylococcus aureus: superbug, super genome? Trends Microbiol. *12*, 378–385. https://doi.org/10.1016/j.tim.2004.06.004.

91. Shettigar, K., and Murali, T.S. (2020). Virulence factors and clonal diversity of Staphylococcus aureus in colonization and wound infection with emphasis on diabetic foot infection. Eur. J. Clin. Microbiol. Infect. Dis. *39*, 2235–2246. https://doi.org/10.1007/s10096-020-03984-8.

92. DuMont, A.L., Nygaard, T.K., Watkins, R.L., Smith, A., Kozhaya, L., Kreiswirth, B.N., Shopsin, B., Unutmaz, D., Voyich, J.M., and Torres, V.J. (2011). Characterization of a new cytotoxin that contributes to Staphylococcus aureus pathogenesis. Mol. Microbiol. *79*, 814–825. https://doi.org/10.1111/j.1365-2958.2010.07490.x.

93. Huseby, M., Shi, K., Brown, C.K., Digre, J., Mengistu, F., Seo, K.S., Bohach, G.A., Schlievert, P.M., Ohlendorf, D.H., and Earhart, C.A. (2007). Structure and biological activities of beta toxin from Staphylococcus aureus. J. Bacteriol. *189*, 8719–8726. https://doi.org/10.1128/JB.00741-07.

94. Johnston, L.J. (2008). Sphingomyelinase generation of ceramide promotes clustering of nanoscale domains in supported bilayer membranes. Biochimica et Biophysica Acta (BBA)-Biomembranes *1778*, 185–197. https://doi.org/10.1016/j.bbamem.2007.09.021.

95. Verdon, J., Girardin, N., Lacombe, C., Berjeaud, J.M., and Héchard, Y. (2009). δ-hemolysin, an update on a membrane-interacting peptide. Peptides *30*, 817–823. https://doi.org/10.1016/j.peptides.2008.12.017.

96. Wang, R., Braughton, K.R., Kretschmer, D., Bach, T.H.L., Queck, S.Y., Li, M., Kennedy, A.D., Dorward, D.W., Klebanoff, S.J., Peschel, A., et al. (2007). Identification of novel cytolytic peptides as key virulence determinants for community-associated MRSA. Nat. Med. *13*, 1510–1514. https://doi.org/10.1038/nm1656.

97. Queck, S.Y., Khan, B.A., Wang, R., Bach, T.H.L., Kretschmer, D., Chen, L., Kreiswirth, B.N., Peschel, A., Deleo, F.R., and Otto, M. (2009). Mobile genetic element-encoded cytolysin connects virulence to methicillin resistance in MRSA. PLoS Pathog. *5*, e1000533. https://doi.org/10.1371/journal.ppat.1000533.

98. Alonzo, F., III, and Torres, V.J. (2014). The bicomponent pore-forming leucocidins of Staphylococcus aureus. Microbiol. Mol. Biol. Rev. *78*, 199–230. https://doi.org/10.1128/MMBR.00055-13.

99. Vandenesch, F., Lina, G., and Henry, T. (2012). Staphylococcus aureus hemolysins, bi-component leukocidins, and cytolytic peptides: a redundant arsenal of membrane-damaging virulence factors? Front. Cell. Infect. Microbiol. *2*, 12. https://doi.org/10.3389/fcimb.2012.00012.

100. Imanishi, I., Nicolas, A., Caetano, A.C.B., Castro, T.L.d.P., Tartaglia, N.R., Mariutti, R., Guédon, E., Even, S., Berkova, N., Arni, R.K., et al. (2019). Exfoliative toxin E, a new Staphylococcus aureus virulence factor with host-specific activity. Sci. Rep. *9*, 16336. https://doi.org/10.1038/s41598-019-52777-3.

101. Nishifuji, K., Sugai, M., and Amagai, M. (2008). Staphylococcal exfoliative toxins:"molecular scissors" of bacteria that attack the cutaneous defense barrier in mammals. J. Dermatol. Sci. *49*, 21–31. https://doi.org/10.1016/j.jdermsci.2007.05.007.

102. Mariutti, R.B., Tartaglia, N.R., Seyffert, N., de Paula Castro, T.L., Arni, R.K., Azevedo, V.A., Le Loir, Y., and Nishifuji, K. (2017). Exfoliative toxins of Staphylococcus aureus. In The Rise of Virulence and Antibiotic Resistance in Staphylococcus aureus, S. Enany and L.E.C. Alexander, eds.. https://doi.org/10.5772/66528.

103. Garbacz, K., Piechowicz, L., and Mroczkowska, A. (2015). Distribution of toxin genes among different spa types and phage types of animal Staphylococcus aureus. Arch. Microbiol. *197*, 935–940. https://doi.org/10.1007/s00203-015-1127-y.

104. Motoshima, M., Yanagihara, K., Morinaga, Y., Matsuda, J., Sugahara, K., Yamada, Y., Kohno, S., and Kamihira, S. (2010). Genetic diagnosis of community-acquired MRSA: a multiplex real-time PCR method for Staphylococcal cassette chromosome mec typing and detecting toxin genes. Tohoku J. Exp. Med. *220*, 165–170. https://doi.org/10.1620/tjem.220.165.

105. Nakaminami, H., Noguchi, N., Ikeda, M., Hasui, M., Sato, M., Yamamoto, S., Yoshida, T., Asano, T., Senoue, M., and Sasatsu, M. (2008). Molecular epidemiology and antimicrobial susceptibilities of 273 exfoliative toxin-encoding-gene-positive Staphylococcus aureus isolates from patients with impetigo in Japan. J. Med. Microbiol. *57*, 1251–1258. https://doi.org/10.1099/jmm.0.2008/002824-0.

106. Dicks, J., Turnbull, J.D., Russell, J., Parkhill, J., and Alexander, S. (2021). Genome sequencing of a historic Staphylococcus aureus collection reveals new enterotoxin genes and sheds light on the evolution and genomic organization of this key virulence gene family. J. Bacteriol. *203*, e00587-20. https://doi.org/10.1128/jb.00587-20.

107. Fisher, E.L., Otto, M., and Cheung, G.Y.C. (2018). Basis of virulence in enterotoxin-mediated staphylococcal food poisoning. Front. Microbiol. *9*, 436. https://doi.org/10.3389/fmicb.2018.00436.

108. Ono, H.K., Suzuki, Y., Hirose, S., and Hu, D.L. (2025). Characterization of non-classical staphylococcal enterotoxins SEIJ and SEIW: biological activities and stability. Microbe *8*, 100462. https://doi.org/10.1016/j.microb.2025.100462.

109. Nakane, A., and Asano, K. (2024). Staphylococcus Aureus: Interplay between Bacteria and Hosts (Springer Nature).

110. Fleischer, B., and Schrezenmeier, H. (1988). T cell stimulation by staphylococcal enterotoxins. Clonally variable response and requirement for major histocompatibility complex class II molecules on accessory or target cells. J. Exp. Med. *167*, 1697–1707. https://doi.org/10.1084/jem.167.5.1697.

111. Rigi, G., Ghaedmohammadi, S., and Ahmadian, G. (2019). A comprehensive review on staphylococcal protein A (SpA): Its production and applications. Biotechnol. Appl. Biochem. *66*, 454–464. https://doi.org/10.1002/bab.1742.

112. Kane, T.L., Car, K.E., and Lee, S.W. (2018). Virulence factor targeting of the bacterial pathogen Staphylococcus aureus for vaccine and therapeutics. Curr. Drug Targets *19*, 111–127. https://doi.org/10.2174/1389450117666161128123536.

113. Smith, E.J., Visai, L., Kerrigan, S.W., Speziale, P., and Foster, T.J. (2011). The Sbi protein is a multifunctional immune evasion factor of Staphylococcus aureus. Infect. Immun. *79*, 3801–3809. https://doi.org/10.1128/IAI.05075-11.

114. Zhang, X., Xiong, T., Gao, L., Wang, Y., Liu, L., Tian, T., Shi, Y., Zhang, J., Zhao, Z., Lu, D., et al. (2022). Extracellular fibrinogen-binding protein released by intracellular Staphylococcus aureus suppresses host immunity by targeting TRAF3. Nat. Commun. *13*, 5493. https://doi.org/10.1038/s41467-022-33205-z.

115. Colque-Navarro, P., Palma, M., Söderquist, B., Flock, J.I., and Möllby, R. (2000). Antibody responses in patients with staphylococcal septicemia against two Staphylococcus aureus fibrinogen binding proteins: clumping factor and an extracellular fibrinogen binding protein. Clin. Diagn. Lab. Immunol. *7*, 14–20. https://doi.org/10.1128/CDLI.7.1.14-20.2000.

116. Algammal, A.M., Hetta, H.F., Elkelish, A., Alkhalifah, D.H.H., Hozzein, W.N., Batiha, G.E.S., El Nahhas, N., and Mabrok, M.A. (2020). Methicillin-Resistant Staphylococcus aureus (MRSA): one health perspective approach to the bacterium epidemiology, virulence factors, antibiotic-resistance, and zoonotic impact. Infect. Drug Resist. *13*, 3255–3265. https://doi.org/10.2147/IDR.S272733.

117. Herman-Bausier, P., Valotteau, C., Pietrocola, G., Rindi, S., Alsteens, D., Foster, T.J., Speziale, P., and Dufrêne, Y.F. (2016). Mechanical strength and inhibition of the Staphylococcus aureus collagen-binding protein Cna. mBio *7*, e01529-16. https://doi.org/10.1128/mbio.01529-16.

118. Valenciano-Bellido, S., Caaveiro, J.M.M., Nakakido, M., Kuroda, D., Aikawa, C., Nakagawa, I., and Tsumoto, K. (2023). Targeting hemoglobin receptors IsdH and IsdB of Staphylococcus aureus with a single VHH antibody inhibits bacterial growth. J. Biol. Chem. *299*, 104927. https://doi.org/10.1016/j.jbc.2023.104927.

119. Speziale, P., and Pietrocola, G. (2020). The multivalent role of fibronectin-binding proteins A and B (FnBPA and FnBPB) of Staphylococcus aureus in host infections. Front. Microbiol. *11*, 2054. https://doi.org/10.3389/fmicb.2020.02054.

120. Mills, K.B., Maciag, J.J., Wang, C., Crawford, J.A., Enroth, T.J., Keim, K.C., Dufrêne, Y.F., Robinson, D.A., Fey, P.D., Herr, A.B., and Horswill, A.R. (2024). Staphylococcus aureus skin colonization is mediated by SasG lectin variation. Cell Rep. *43*, 114022. https://doi.org/10.1016/j.celrep.2024.114022.

121. Khandke, L., Nonoyama, A., Hodge, T.S., and Nema, S. (2013). Stable Immunogenic Compositions of Staphylococcus aureus Antigens (Google Patents).

122. Peng, Q., Tang, X., Dong, W., Sun, N., and Yuan, W. (2022). A review of biofilm formation of Staphylococcus aureus and its regulation mechanism. Antibiotics *12*, 12. https://doi.org/10.3390/antibiotics12010012.

123. Ríos-López, A.L., González, G.M., Hernández-Bello, R., and Sánchez-González, A. (2021). Avoiding the trap: Mechanisms developed by pathogens to escape neutrophil extracellular traps. Microbiol. Res. *243*, 126644. https://doi.org/10.1016/j.micres.2020.126644.

124. Lister, J.L., and Horswill, A.R. (2014). Staphylococcus aureus biofilms: recent developments in biofilm dispersal. Front. Cell. Infect. Microbiol. *4*, 178. https://doi.org/10.3389/fcimb.2014.00178.

125. Howden, B.P., Giulieri, S.G., Wong Fok Lung, T., Baines, S.L., Sharkey, L.K., Lee, J.Y.H., Hachani, A., Monk, I.R., and Stinear, T.P. (2023). Staphylococcus aureus host interactions and adaptation. Nat. Rev. Microbiol. *21*, 380–395. https://doi.org/10.1038/s41579-023-00852-y.

126. Bhattacharya, M., Berends, E.T.M., Zheng, X., Hill, P.J., Chan, R., Torres, V.J., and Wozniak, D.J. (2020). Leukocidins and the nuclease nuc prevent neutrophil-mediated killing of Staphylococcus aureus biofilms. Infect. Immun. *88*, e00372-20. https://doi.org/10.1128/iai.00372-20.

127. Ji, G., Beavis, R., and Novick, R.P. (1997). Bacterial interference caused by autoinducing peptide variants. Science *276*, 2027–2030. https://doi.org/10.1126/science.276.5321.2027.

128. Foster, T.J., Geoghegan, J.A., Ganesh, V.K., and Höök, M. (2014). Adhesion, invasion and evasion: the many functions of the surface proteins of Staphylococcus aureus. Nat. Rev. Microbiol. *12*, 49–62. https://doi.org/10.1038/nrmicro3161.

129. Petit, R.A., 3rd, and Read, T.D. (2018). Staphylococcus aureus viewed from the perspective of 40,000+ genomes. PeerJ *6*, e5261. https://doi.org/10.7717/peerj.5261.

130. Garzoni, C., and Kelley, W.L. (2009). Staphylococcus aureus: new evidence for intracellular persistence. Trends Microbiol. *17*, 59–65. https://doi.org/10.1016/j.tim.2008.11.005.

131. Spaan, A.N., Surewaard, B.G.J., Nijland, R., and van Strijp, J.A.G. (2013). Neutrophils versus Staphylococcus aureus: a biological tug of war. Annu. Rev. Microbiol. *67*, 629–650. https://doi.org/10.1146/annurev-micro-092412-155746.

132. Stapels, D.A.C., Ramyar, K.X., Bischoff, M., von Köckritz-Blickwede, M., Milder, F.J., Ruyken, M., Eisenbeis, J., McWhorter, W.J., Herrmann, M., van Kessel, K.P.M., et al. (2014). Staphylococcus aureus secretes a unique class of neutrophil serine protease inhibitors. Proc. Natl. Acad. Sci. USA *111*, 13187–13192. https://doi.org/10.1073/pnas.1407616111.

133. Kretschmer, D., Breitmeyer, R., Gekeler, C., Lebtig, M., Schlatterer, K., Nega, M., Stahl, M., Stapels, D., Rooijakkers, S., and Peschel, A. (2021). Staphylococcus aureus depends on Eap proteins for preventing degradation of its phenol-soluble modulin toxins by neutrophil serine proteases. Front. Immunol. *12*, 701093. https://doi.org/10.3389/fimmu.2021.701093.

134. Cheung, G.Y.C., Bae, J.S., and Otto, M. (2021). Pathogenicity and virulence of Staphylococcus aureus. Virulence *12*, 547–569. https://doi.org/10.1080/21505594.2021.1878688.

135. de Jong, N.W.M., Ramyar, K.X., Guerra, F.E., Nijland, R., Fevre, C., Voyich, J.M., McCarthy, A.J., Garcia, B.L., van Kessel, K.P.M., van Strijp, J.A.G., et al. (2017). Immune evasion by a staphylococcal inhibitor of myeloperoxidase. Proc. Natl. Acad. Sci. USA *114*, 9439–9444. https://doi.org/10.1073/pnas.1707032114.

136. Lin, W., Chen, H., Chen, X., and Guo, C. (2024). The roles of neutrophil-derived myeloperoxidase (MPO) in diseases: The new progress. Antioxidants *13*, 132. https://doi.org/10.3390/antiox13010132.

137. Buchan, K.D., Foster, S.J., and Renshaw, S.A. (2019). Staphylococcus aureus: setting its sights on the human innate immune system. Microbiology *165*, 367–385. https://doi.org/10.1099/mic.0.000759.

138. de Jong, N.W.M., van Kessel, K.P.M., and van Strijp, J.A.G. (2019). Immune evasion by Staphylococcus aureus. Microbiol. Spectr. *7*. https://doi.org/10.1128/microbiolspec.gpp3-0061-2019.

139. Meyers, S., Crescente, M., Verhamme, P., and Martinod, K. (2022). Staphylococcus aureus and neutrophil extracellular traps: the master manipulator meets its match in immunothrombosis. Arterioscler. Thromb. Vasc. Biol. *42*, 261–276. https://doi.org/10.1161/ATVBAHA.121.316930.

140. von Köckritz-Blickwede, M., and Winstel, V. (2022). Molecular prerequisites for neutrophil extracellular trap formation and evasion mechanisms of Staphylococcus aureus. Front. Immunol. *13*, 836278. https://doi.org/10.3389/fimmu.2022.836278.

141. de Vor, L., Rooijakkers, S.H.M., and van Strijp, J.A.G. (2020). Staphylococci evade the innate immune response by disarming neutrophils and forming biofilms. FEBS Lett. *594*, 2556–2569. https://doi.org/10.1002/1873-3468.13767.

142. Speziale, P., and Pietrocola, G. (2021). Staphylococcus aureus induces neutrophil extracellular traps (NETs) and neutralizes their bactericidal potential. Comput. Struct. Biotechnol. J. *19*, 3451–3457. https://doi.org/10.1016/j.csbj.2021.06.012.

143. Hartman-Adams, C.B., and Jucket, G.. Impetigo: diagnosis and treatment. https://www.aafp.org/pubs/afp/issues/2014/0815/p229.html.

144. Galindo, A., and Hebert, A.A. (2021). A comparative review of current topical antibiotics for impetigo. Expert Opin. Drug Saf. *20*, 677–683. https://doi.org/10.1080/14740338.2021.1902502.

145. Gahlawat, W.T., Bushell, M., Abrha, S., Peterson, G.M., Mathew, C., Sinnollareddy, M., McMillan, F., Samarawickrema, I., Calma, T., Chang, A.Y., et al. (2021). Emerging Treatment Strategies for Impetigo in Endemic and Nonendemic Settings: A Systematic Review. Clin. Ther. *43*, 986–1006. https://doi.org/10.1016/j.clinthera.2021.04.013.

146. Yang, L.P.H., and Keam, S.J. (2008). Retapamulin: a review of its use in the management of impetigo and other uncomplicated superficial skin infections. Drugs *68*, 855–873. https://doi.org/10.2165/00003495-200868060-00008.

147. Wang, Z., Feig, J.L., Mannschreck, D.B., and Cohen, B.A. (2020). Antibiotic sensitivity and clinical outcomes in staphylococcal scalded skin syndrome. Pediatr. Dermatol. *37*, 222–223. https://doi.org/10.1111/pde.14014.

148. Ladhani, S., Robbie, S., Chapple, D.S., Joannou, C.L., and Evans, R.W. (2003). Isolating Staphylococcus aureus from children with suspected staphylococcal scalded skin syndrome is not clinically useful. Pediatr. Infect. Dis. J. *22*, 284–286.

149. Neubauer, H.C., Hall, M., Lopez, M.A., Cruz, A.T., Queen, M.A., Foradori, D.M., Aronson, P.L., Markham, J.L., Nead, J.A., Hester, G.Z., et al. (2021). Antibiotic Regimens and Associated Outcomes in Children Hospitalized With Staphylococcal Scalded Skin Syndrome. J. Hosp. Med. *16*, 149–155. https://doi.org/10.12788/jhm.3529.

150. Boyce, B.J., and deSilva, B.W. (2014). Spontaneous MRSA postcricoid abscess: A case report and literature review. Laryngoscope *124*, 2583–2585. https://doi.org/10.1002/lary.24819.

151. Baumgartner, J.C., and Xia, T. (2003). Antibiotic Susceptibility of Bacteria Associated with Endodontic Abscesses. J. Endod. *29*, 44–47. https://doi.org/10.1097/00004770-200301000-00012.

152. Angelopoulou, A., Field, D., Ryan, C.A., Stanton, C., Hill, C., and Ross, R.P. (2018). The microbiology and treatment of human mastitis. Med. Microbiol. Immunol. *207*, 83–94. https://doi.org/10.1007/s00430-017-0532-z.

153. Algammal, A.M., Hetta, H.F., Elkelish, A., Alkhalifah, D.H.H., Hozzein, W.N., Batiha, G.E.S., El Nahhas, N., and Mabrok, M.A. (2020). Methicillin-Resistant Staphylococcus aureus (MRSA): One Health Perspective Approach to the Bacterium Epidemiology, Virulence Factors, Antibiotic-Resistance, and Zoonotic Impact. Infect. Drug Resist. *13*, 3255–3265. https://doi.org/10.2147/IDR.S272733.

154. Leiblein, M., Marzi, I., Sander, A.L., Barker, J.H., Ebert, F., and Frank, J. (2018). Necrotizing fasciitis: treatment concepts and clinical results. Eur. J. Trauma Emerg. Surg. *44*, 279–290. https://doi.org/10.1007/s00068-017-0792-8.

155. Öztürk, A.M., Akyol, D., Süer, O., Erdem, H.A., Şimşir, I.Y., Akar, Ş.Ş., Özkayin, N., and Taşbakan, M.I. (2019). Necrotising fasciitis: clinical evaluation and treatment results of 18 Patients. Mediterr. J. Infect. Microb. Antimicrob. *8*, 9. https://doi.org/10.4274/mjima.galenos.2019.2019.9.

156. Kumar, A., Shah, N.P., Menon, V., and Nissen, S.E. (2019). Purpura fulminans manifesting with Staphylococcus aureus endocarditis: a case report. Eur. Heart J. Case Rep. *3*, ytz077. https://doi.org/10.1093/ehjcr/ytz077.

157. Prabhoo, R., Chaddha, R., Iyer, R., Mehra, A., Ahdal, J., and Jain, R. (2019). Overview of methicillin resistant Staphylococcus aureus mediated bone and joint infections in India. Orthop. Rev. *11*, 8070. https://doi.org/10.4081/or.2019.8070.

158. Cortés-Penfield, N.W., and Kulkarni, P.A. (2019). The History of Antibiotic Treatment of Osteomyelitis. Open Forum Infect. Dis. *6*, ofz181. https://doi.org/10.1093/ofid/ofz181.

159. John Scott Earwood, M., Tyler, R., Walker, M.D., and SUE, G.J.C. (2021). Septic Arthritis: Diagnosis and Treatment. Am. Fam. Physician. *104*, 589–597. https://www.aafp.org/pubs/afp/issues/2021/1200/p589.html.

160. Martínez-Aguilar, G., Hammerman, W.A., Mason, E.O., Jr., and Kaplan, S.L. (2003). Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus in children. Pediatr. Infect. Dis. J. *22*, 593–598. https://doi.org/10.1097/01.inf.0000073163.37519.ee.

161. Mendes, R.E., Deshpande, L.M., Smyth, D.S., Shopsin, B., Farrell, D.J., and Jones, R.N. (2012). Characterization of Methicillin-Resistant Staphylococcus aureus Strains Recovered from a Phase IV Clinical Trial for Linezolid versus Vancomycin for Treatment of Nosocomial Pneumonia. J. Clin. Microbiol. *50*, 3694–3702. https://doi.org/10.1128/JCM.02024-12.

162. Parsons, J.B., Westgeest, C.A., Conlon, B.P., and Fowler, V.G. (2023). Persistent Methicillin-Resistant Staphylococcus aureus Bacteremia: Host, Pathogen, and Treatment. Antibiotics (Basel) *12*, 455. https://doi.org/10.3390/antibiotics12030455.

163. Eckmann, C., and Dryden, M. (2010). Treatment of complicated skin and soft-tissue infections caused by resistant bacteria: value of linezolid, tigecycline, daptomycin and vancomycin. Eur. J. Med. Res. *15*, 554–563. https://doi.org/10.1186/2047-783x-15-12-554.

164. Huerta, L.E., and Rice, T.W. (2019). Pathologic Difference between Sepsis and Bloodstream Infections. J. Appl. Lab. Med. *3*, 654–663. https://doi.org/10.1373/jalm.2018.026245.

165. Brown, N.M., Goodman, A.L., Horner, C., Jenkins, A., and Brown, E.M. (2021). Treatment of methicillin-resistant Staphylococcus aureus (MRSA): updated guidelines from the UK. JAC. Antimicrob. Resist. *3*, dlaa114. https://doi.org/10.1093/jacamr/dlaa114.

166. Chuang, C.C., Hsiao, C.H., Tan, H.Y., Ma, D.H., Lin, K.K., Chang, C.J., and Huang, Y.C. (2012). Staphylococcus aureus Ocular Infection: Methicillin-Resistance, Clinical Features, and Antibiotic Susceptibilities. PLoS One *8*, e42437. https://doi.org/10.1371/journal.pone.0042437.

167. Antonello, R.M., and Riccardi, N. (2022). How we deal with Staphylococcus aureus (MSSA, MRSA) central nervous system infections. Front Biosci (Schol Ed) *14*, 1. https://doi.org/10.31083/j.fbs1401001.

168. Mitiku, A., Aklilu, A., Biresaw, G., and Gize, A. (2021). Prevalence and Associated Factors of Methicillin Resistance Staphylococcus aureus (MRSA) Among Urinary Tract Infection Suspected Patients Attending at Arba Minch General Hospital, Southern Ethiopia. Infect. Drug Resist. *14*, 2133–2142. https://doi.org/10.2147/IDR.S306648.

169. Bayer, A.S., Bolger, A.F., Taubert, K.A., Wilson, W., Steckelberg, J., Karchmer, A.W., Levison, M., Chambers, H.F., Dajani, A.S., Gewitz, M.H., et al. (1998). Diagnosis and Management of Infective Endocarditis and Its Complications. Circulation *98*, 2936–2948. https://doi.org/10.1161/01.cir.98.25.2936.

170. Cuervo, G., Escrihuela-Vidal, F., Gudiol, C., and Carratalà, J. (2021). Current Challenges in the Management of Infective Endocarditis. Front. Med. *8*, 641243. https://doi.org/10.3389/fmed.2021.641243.

171. Das, I., Saluja, T., and Steeds, R. (2011). Use of daptomycin in complicated cases of infective endocarditis. Eur. J. Clin. Microbiol. Infect. Dis. *30*, 807–812. https://doi.org/10.1007/s10096-011-1160-y.

172. Kullar, R., Casapao, A.M., Davis, S.L., Levine, D.P., Zhao, J.J., Crank, C.W., Segreti, J., Sakoulas, G., Cosgrove, S.E., and Rybak, M.J. (2013). A multicentre evaluation of the effectiveness and safety of high-dose daptomycin for the treatment of infective endocarditis.

J. Antimicrob. Chemother. *68*, 2921–2926. https://doi.org/10.1093/jac/dkt294.

173. Browne, C., Muszbek, N., Chapman, R., Marsh, K., Gould, I.M., Seaton, R.A., and Allen, M. (2016). Comparative healthcare-associated costs of methicillin-resistant Staphylococcus aureus bacteraemia-infective endocarditis treated with either daptomycin or vancomycin. Int. J. Antimicrob. Agents *47*, 357–361. https://doi.org/10.1016/j.ijantimicag.2016.02.006.

174. Martin, J.H., Norris, R., Barras, M., Roberts, J., Morris, R., Doogue, M., and Jones, G.R.D. (2010). Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society Of Infectious Diseases Pharmacists. Clin. Biochem. Rev. *31*, 21–24.

175. Anpalagan, K., Dotel, R., MacFadden, D.R., Smith, S., Voss, L., Petersiel, N., Marks, M., Marsh, J., Mahar, R.K., McGlothlin, A., et al. (2024). Does adjunctive clindamycin have a role in Staphylococcus aureus bacteremia? A protocol for the adjunctive treatment domain of the Staphylococcus aureus Network Adaptive Platform (SNAP) randomized controlled trial. Clin. Infect. Dis. *79*, 626–634. https://doi.org/10.1093/cid/ciae289.

176. Visperas, A., Santana, D., Klika, A.K., Higuera-Rueda, C.A., and Piuzzi, N.S. (2022). Current treatments for biofilm-associated periprosthetic joint infection and new potential strategies. J. Orthop. Res. *40*, 1477–1491. https://doi.org/10.1002/jor.25345.

177. Torres, A., Kuraieva, A., Stone, G.G., and Cillóniz, C. (2023). Systematic review of ceftaroline fosamil in the management of patients with methicillin-resistant Staphylococcus aureus pneumonia. Eur. Respir. Rev. *32*, 230117. https://doi.org/10.1183/16000617.0117-2023.

178. Rolston, K., Gerges, B., Nesher, L., Shelburne, S.A., Prince, R., and Raad, I. (2023). In vitro activity of eravacycline and comparator agents against bacterial pathogens isolated from patients with cancer. JAC. Antimicrob. Resist. *5*, dlad020. https://doi.org/10.1093/jacamr/dlad020.

179. Liang, W., Yin, H., Chen, H., Xu, J., and Cai, Y. (2024). Efficacy and safety of omadacycline for treating complicated skin and soft tissue infections: a meta-analysis of randomized controlled trials. BMC Infect. Dis. *24*, 219. https://doi.org/10.1186/s12879-024-09097-3.

180. Lan, S.-H., Lin, W.T., Chang, S.P., Lu, L.C., Chao, C.M., Lai, C.C., and Wang, J.H. (2019). Tedizolid versus linezolid for the treatment of acute bacterial skin and skin structure infection: a systematic review and meta-analysis. Antibiotics *8*, 137. https://doi.org/10.3390/antibiotics8030137.

181. Zhang, C., Zhao, W., Bian, C., Hou, X., Deng, B., McComb, D.W., Chen, X., and Dong, Y. (2019). Antibiotic-derived lipid nanoparticles to treat intracellular Staphylococcus aureus. ACS Appl. Bio Mater. *2*, 1270–1277. https://doi.org/10.1021/acsabm.8b00821.

182. Norrrahim, M.N.F., Nurazzi, N.M., Jenol, M.A., Farid, M.A.A., Janudin, N., Ujang, F.A., Yasim-Anuar, T.A.T., Syed Najmuddin, S.U.F., and Ilyas, R.A. (2021). Emerging development of nanocellulose as an antimicrobial material: An overview. Mater. Adv. *2*, 3538–3551. https://doi.org/10.1039/D1MA00116G.

183. Fahimirad, S., Abtahi, H., Satei, P., Ghaznavi-Rad, E., Moslehi, M., and Ganji, A. (2021). Wound healing performance of PCL/chitosan based electrospun nanofiber electrosprayed with curcumin loaded chitosan nanoparticles. Carbohydr. Polym. *259*, 117640. https://doi.org/10.1016/j.carbpol.2021.117640.

184. Vijayakumar, S., Malaikozhundan, B., Parthasarathy, A., Saravanakumar, K., Wang, M.H., and Vaseeharan, B. (2020). Nano biomedical potential of biopolymer chitosan-capped silver nanoparticles with special reference to antibacterial, antibiofilm, anticoagulant and wound dressing material. J. Clust. Sci. *31*, 355–366. https://doi.org/10.1007/s10876-019-01649-x.

185. Lu, H., Butler, J.A., Britten, N.S., Venkatraman, P.D., and Rahatekar, S.S. (2021). Natural antimicrobial nano composite fibres manufactured from a combination of alginate and oregano essential oil. Nanomaterials *11*, 2062. https://doi.org/10.3390/nano11082062.

186. Ye, J., Hou, F., Chen, G., Zhong, T., Xue, J., Yu, F., Lai, Y., Yang, Y., Liu, D., Tian, Y., and Huang, J. (2023). Novel copper-containing ferrite nanoparticles exert lethality to MRSA by disrupting MRSA cell membrane permeability, depleting intracellular iron ions, and upregulating ROS levels. Front. Microbiol. *14*, 1023036. https://doi.org/10.3389/fmicb.2023.1023036.

187. Yuan, Q., Zhao, Y., Zhang, Z., and Tang, Y. (2021). On-demand antimicrobial agent release from functionalized conjugated oligomer-hyaluronic acid nanoparticles for tackling antimicrobial resistance. ACS Appl. Mater. Interfaces *13*, 257–265. https://doi.org/10.1021/acsami.0c19283.

188. Wang, P., Jiang, S., Li, Y., Luo, Q., Lin, J., Hu, L., Liu, X., and Xue, F. (2021). Virus-like mesoporous silica-coated plasmonic Ag nanocube with strong bacteria adhesion for diabetic wound ulcer healing. Nanomedicine. *34*, 102381. https://doi.org/10.1016/j.nano.2021.102381.

189. Nandhini, P., Kumar, P., Mickymaray, S., Alothaim, A.S., Somasundaram, J., and Rajan, M. (2022). Recent Developments in Methicillin-Resistant Staphylococcus aureus (MRSA) Treatment: A Review. Antibiotics (Basel) *11*, 606. https://doi.org/10.3390/antibiotics11050606.

190. Dong, P.T., Mohammad, H., Hui, J., Leanse, L.G., Li, J., Liang, L., Dai, T., Seleem, M.N., and Cheng, J.X. (2019). Photolysis of Staphyloxanthin in methicillin-resistant Staphylococcus aureus potentiates killing by reactive oxygen species. Adv. Sci. *6*, 1900030. https://doi.org/10.1002/advs.201900030.