REVIEW

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Methicillin-Resistant Staphylococcus Aureus in orthopedic surgery: Current evidence from diagnosis until rehabilitative management

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ABSTRACT

Background: Methicillin-resistant Staphylococcus aureus (MRSA) is a significant threat in orthopaedic surgery. This study aimed to evaluate the current evidence from diagnosis to rehabilitative management of MRSA in orthopedic surgery
Methods: This narrative overview synthesized current evidence across the care pathway in orthopaedics, epidemiology and pathogenesis (including key resistance/virulence determinants), diagnostic approaches (sampling strategies and rapid molecular tests), therapeutic strategies (surgery plus tailored antimicrobials and local delivery), rehabilitation considerations, prevention and stewardship programs, and emerging modalities (new antibiotics, bacteriophages, and nanotechnology-enabled delivery).
Results: MRSA resistance is primarily mediated by mecA (PBP2a) and augmented by additional virulence factors (e.g., panton-valentine leukocidin). Biofilm on orthopaedic implants protects bacteria from host defences and antibiotics, underpinning recurrent infection. Diagnostic yield improves with deep tissue or implant-associated sampling, while polymerase chain reaction expedites detection of resistance genes to guide early management. Optimal treatment typically combines surgical debridement with implant retention or exchange where appropriate and prolonged, targeted antimicrobials; adjuncts include local antibiotic carriers and negative-pressure wound strategies. Innovative options—novel agents, bacteriophage therapy, and nanotechnology-based delivery—show promise in early studies.
Conclusion: Integrated programs, preoperative screening/decolonization, risk-adapted prophylaxis, and antimicrobial stewardship have helped lower MRSA infection rates, yet biofilm biology and rising resistance sustain a substantial burden. Emerging options include linezolid/tedizolid or minocycline plus rifampicin, with efficacy superior to vancomycin, bacteriophage therapy as an adjunct in refractory prosthetic joint infections, and nanotechnology-enabled implant coatings to deter biofilm formation.

Keywords: Current diagnosis MRSA, Methicillin-Resistant Staphylococcus aureus, orthopaedics, rehabilitative management.
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INTRODUCTION

Methicillin-resistant Staphylococcus aureus (MRSA) infection is a major global public-health problem due to its resistance to multiple antibiotic classes. The global prevalence of MRSA varies by region and population group. The estimated prevalence of the general population is 5.8%.[1] Elderly individuals residing in long-term care facilities had a higher prevalence of 14.7%.[2] In the child population, it is approximately 5%, and patients with HIV infection reach 7%, with Southeast Asia among the regions with the greatest burden.[3,4]

In orthopaedic surgery, MRSA has its prominent effect on surgical site infections (SSIs). S. aureus is the most culture-confirmed SSI (48.0%). The incidence of S. aureus infection has been reported at 1.13%, with MRSA as the causative agent accounting for 44–46% of these cases.[5] In orthopaedic practice, community-acquired (CA) MRSA often carries panton-valentine leukocidin (PVL) and is linked to aggressive skin/soft tissue infections and abscesses, whereas hospital-acquired (HA) MRSA predominates around implants, influenced by healthcare exposure and patient comorbidity profiles; risks include recent hospitalization, nursing-home residence, prior broad-spectrum antibiotics, diabetes, obesity, smoking, and malnutrition.[6-15] This epidemiologic split has implications for screening, prophylaxis, and empiric therapy.

Orthopaedic procedures frequently

involve implants such as plates, screws, and prosthetic devices, which provide an ideal surface for bacterial adhesion and biofilm formation. Biofilms markedly complicate eradication, leading to persistent or recurrent infections.[6] Moreover, prolonged operative duration and the involvement of bone and joint tissues increase the risk of deep and difficult-to-treat infections.

Based on those mentioned above, this review aims to update the current evidence on the epidemiology, pathogenesis, clinical spectrum, diagnosis, management, and prevention of MRSA infections in orthopaedic surgery, while highlighting ongoing challenges and emerging future directions.

SEARCH STRATEGY AND SELECTION CRITERIA

We conducted a narrative literature search (January 2003–September 2025) across PubMed/MEDLINE, Cochrane Library, and major orthopaedic/infectious diseases journals focusing on MRSA in orthopaedic surgery. Search terms included 'MRSA', 'orthopaedic', 'prosthetic joint infection', 'biofilm', 'screening', 'decolonization', 'prophylaxis', 'PCR', 'phage', and 'nanocoating'. Inclusion criteria: clinical studies, systematic reviews/meta-analyses, guidelines, or large cohorts relevant to epidemiology, diagnosis, treatment (surgery/antimicrobials/local delivery/NPWT), prevention, rehabilitation, and emerging therapies. Exclusion criteria: non-English, non-human, or studies without orthopaedic relevance. Selection prioritized higher-level evidence (systematic reviews, multicentre cohorts, guideline statements). Data were extracted on setting, design, key outcomes, and applicability to orthopaedic decision-making.

EPIDEMIOLOGY AND RISK FACTORS OF MRSA IN ORTHOPEDIC SURGERY

The epidemiology of MRSA infection in orthopaedic surgery demonstrates wide variation across patient populations, surgical settings, and geographic regions. In acute fracture care, the reported MRSA colonization rate is 1.4%, whereas patients undergoing elective surgery in nonunion, malunion, revision procedures, or implant removal exhibit markedly higher colonization rates, reaching 15.4%.[7] The burden of MRSA in SSIs has remained relatively stable over recent years. A study in Japan showed MRSA accounted for 0.12% of SSIs before 2020 compared to 0.17% after 2020, reflecting only a slight increase.[8] A multicenter study in Southeast Asia reported that MRSA infections accounted for 27% of orthopaedic infections, compared to only 5.77% in Canada, which highlights a significantly higher prevalence in low- and middle-income regions.[9]

Nasal or skin colonization with MRSA is recognized as an independent predictor of postoperative MRSA infection. MRSA carriers demonstrate a significantly increased risk of developing SSIs (OR = 3.4 - 11) compared to non-carriers.[10-12] Importantly, even after apparently successful decolonization, MRSA carriage may reflect a broader vulnerability to infection or incomplete eradication. During surgical procedures, endogenous colonization serves as a direct source for bacterial seeding into wounds and implant surfaces, where biofilm formation further complicates eradication.

Other factors related to MRSA infection are healthcare exposure, patient-related, and wound-related factors. Recent hospitalization has been associated with approximately a 1.8-fold increased risk, while nursing home residence carries an even higher risk (OR 8.42).[10,13] Prior use of broad-spectrum antibiotics and prolonged preoperative stays further promote MRSA survival and surgical site infection.[10] Patient-related risks include advanced age, diabetes mellitus, obesity, smoking, and immunocompromised states such as chronic renal failure or corticosteroid use.[10,14] Malnutrition, particularly hypoalbuminemia, nearly doubles infection risk (OR 1.96), while obesity (41.76% vs. 34.67%), smoking (33.36% vs. 19.73%), and diabetes (25.06% vs. 19.85%) are significantly more prevalent in MRSA-infected patients.[14,15] Wound-related factors are equally critical: open wounds increase infection nearly sixfold (OR 5.97), and excessive blood loss, prolonged operations, revision surgeries, and implants predispose to infection through biofilm formation.[10,15]

PATHOGENESIS AND MECHANISMS OF RESISTANCE

Staphylococcus aureus is a versatile pathogen capable of acquiring multiple resistance determinants, with MRSA posing a major clinical threat. Several genes, including mec, fem, van, staphylococcal protein A (SPA), PVL, and gamma-hemolysin (HLG), mediate resistance and virulence.

MEC GENES (MECA, MECB, MECC)

The primary determinant of methicillin resistance in Staphylococcus aureus is the mecA gene, located on the staphylococcal cassette chromosome mec (SCCmec). mecA encodes penicillin-binding protein 2a (PBP2a), which has low affinity for β-lactam antibiotics, rendering them ineffective.[16] Alternative variants such as mecB and mecC have also been described, further expanding the genetic diversity of MRSA strains.[17]

FEMA GENE

The femA gene, part of the femAB operon, is essential for methicillin resistance by facilitating pentaglycine cross-linking in peptidoglycan synthesis. Although not a direct resistance gene, it acts as an auxiliary factor enhancing the resistance conferred by mecA. Moreover, femA is frequently used as a molecular marker for S. aureus identification in diagnostic assays.[18]

VAN GENES (VANA, VANB)

Resistance to glycopeptides such as vancomycin is mediated by van genes, particularly vanA and vanB. These genes modify peptidoglycan precursors from D-Ala-D-Ala to D-Ala-D-Lac, thereby reducing vancomycin binding affinity.[19] Clinical reports of vancomycin-resistant S. aureus (VRSA) have been increasing, with recent studies detecting vanA and vanB in Nigerian isolates.[20] This highlights the global concern of reduced treatment options for MRSA infections.

SPA GENE

The SPA gene encodes staphylococcal protein A, a surface protein that binds to the Fc portion of IgG, preventing opsonization and phagocytosis. Its polymorphic Xr region contains variable tandem repeats, making it a valuable tool for molecular typing and epidemiological studies.[21]

PVL AND HLG GENES

The PVL gene encodes panton-valentine leukocidin, a pore-forming toxin associated with leukocyte destruction, abscess formation, and severe skin and soft tissue infection.[22] Meanwhile, the HLG gene encodes gamma-hemolysin, another pore-forming cytotoxin that contributes to immune evasion and tissue damage. Both toxins increase MRSA pathogenicity and have been linked to higher morbidity in community-acquired infections.

CLINICAL CONSEQUENCES FOR ORTHOPAEDIC INFECTIONS

Biofilm protects MRSA from immune clearance and antibiotic penetration, explaining the frequent need for implant removal or staged revision in orthopaedic surgery. mecA-mediated resistance alters regulatory pathways, favoring biofilm persistence on implants over acute toxin production. This dual phenotype makes MRSA infections uniquely difficult to eradicate in the orthopaedic setting.[23,24]

DIAGNOSIS OF MRSA IN ORTHOPEDIC INFECTIONS

The diagnostic work-up of orthopaedic infections begins with routine clinical and laboratory evaluation. Clinical suspicion arises from persistent wound drainage, erythema, localized pain, or systemic features of infection, as discussed in the previous section. Laboratory markers such as leukocyte count, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are widely used as supportive indicators but lack specificity for MRSA.[25] Despite these supportive tools, definitive diagnosis rests upon microbiological confirmation. Standard culture remains the gold standard, enabling both pathogen identification and antimicrobial susceptibility profiling. However, culture methods are limited by delayed turnaround time and reduced yield in biofilm-associated infections or in patients already exposed to antibiotics.

CULTURE AND SENSITIVITY

For suspected MRSA infection, tissue biopsy, deep wound specimens, or sonication fluid from removed implants provide the highest diagnostic yield. Culture enables identification of Staphylococcus aureus and determination of methicillin resistance through antimicrobial susceptibility testing.

In addition to obtaining samples directly from the surgical site, current studies show nasal swabs can also serve as a valuable diagnostic and preventive tool. Large cohort studies have shown that nasal colonization with S. aureus is common, with prevalence rates of 26.3% for MSSA and 7.7% for MRSA among orthopedic patients undergoing elective surgery.[26] Similarly, a prospective cohort of 526 orthopedic patients reported that 26.6% were MRSA carriers, who were 3.44 times more likely to develop MRSA-associated SSIs compared to non-carriers.[27]

PCR AND MOLECULAR DIAGNOSTICS

Molecular methods have increasingly complemented traditional culture in detecting MRSA. Polymerase chain reaction (PCR) assays targeting the mecA gene or the penicillin-binding protein 2a (PBP2a) are specific and allow rapid discrimination between MRSA and MSSA.

MRSA PCR testing demonstrates high diagnostic accuracy across clinical settings, with excellent negative predictive values that allow clinicians to de-escalate or withhold empiric MRSA therapy safely.[28-30] In skin and soft tissue infections, PCR wound swabs achieved a sensitivity of 97.6% and an NPV of 98.4%, while in respiratory infections, nasal PCR assays maintained an NPV of 94.9% for up to two weeks.[28,29] In trauma ICU patients, a negative PCR showed an NPV of 100%, effectively ruling out future MRSA infections.[30] While tools such as the GeneXpert® MRSA/SA SSTI test reduce unnecessary broad-spectrum antibiotic use in orthopedic infections, sensitivity may be lower at 42.9% in complex hardware-related cases.[31] Overall, PCR assays represent a reliable adjunct to conventional cultures, improving diagnostic precision and antimicrobial stewardship.[32]

CURRENT MANAGEMENT STRATEGIES

The management of MRSA infections requires a combination of surgical intervention and tailored antimicrobial therapy. A recent study by Scherper suggested that combination therapy can be achieved through a short-term rifampicin strategy with either clindamycin or flucloxacillin and only 5 days of rifampicin.[33]

Debridement, antibiotics, and implant retention (DAIR) are frequently considered for early or acute postoperative infections where biofilm formation is minimal. Aggressive surgical debridement, combined with exchange of modular components and systemic antibiotics, can be adequate if performed promptly. The widely agreed indications for DAIR are a well-fixed prosthesis, no sinus tract, antibiotic-susceptible organisms must be responsible for the infection, and sufficient soft-tissue coverage.[34]

One-stage and two-stage revision are the main surgical strategies for prosthetic joint infection (PJI). One-stage revision is generally reserved for the early postoperative period (within 2 weeks to 3 months) or when symptoms last less than 3 weeks. It is appropriate in patients with good bone stock, healthy soft tissue, absence of sepsis, and an identified pathogen susceptible to effective antibiotics, with extensive debridement and antibiotic-loaded cement fixation forming the core of the procedure. In contrast, two-stage revision is preferred in more complex cases, particularly when soft tissue quality is poor, sepsis or sinus tracts are present, or the pathogen is resistant or unidentified. This approach requires prosthesis removal, spacer placement, and prolonged antibiotic therapy before reimplantation, with timing ranging from weeks to months. Although more invasive and time-consuming, two-stage revision remains the gold standard for challenging

infections, whereas one-stage revision offers faster recovery in carefully selected patients.[34] In situations where infection control cannot be achieved with DAIR or revision strategies, complete implant removal may be necessary.[35]

Treatment strategies vary according to local epidemiology. In specific clinical contexts, monotherapy may be sufficient, whereas in others, combination therapy is recommended. The rationale for combining antibiotics includes broadening antimicrobial coverage, enhancing bactericidal activity, achieving synergistic effects, and improving activity against biofilm, thereby optimizing treatment outcomes.[36]

Local antibiotic delivery is increasingly recognized as a key strategy in MRSA management due to its ability to achieve high local concentrations while minimizing systemic toxicity. Mills et al. reported strong evidence for local therapy in fracture-related infections, particularly in high-risk cases, with adverse events being rare.[37] Madadi et al. analyzed 23 spinal deep surgical site infections treated with antibiotic-loaded PMMA, where vancomycin, ceftriaxone, and ceftazidime peaked at ~15.4% release within 2 days and stabilized at ~3.6% by day 7, successfully controlling infection even in high-risk ASA IV patients.[38] In patients unable to receive vancomycin, Annasamudram et al. documented 13 cases using linezolid-loaded PMMA spacers, with 9 achieving limb salvage and remaining infection-free at a mean of 55.5 months.[39] Innovatively, Puli et al. developed a dual daptomycin-rifampicin titania nanotube implant that significantly reduced MRSA biofilm, accelerated fibroblast proliferation, and enhanced calcium deposition, highlighting its dual antibacterial and osteogenic potential.[40]

Negative pressure wound therapy (NPWT) has become an important adjunct in managing infected orthopedic wounds. A retrospective study reported that a modified NPWT technique with irrigation, combined with antibiotics and debridement, achieved infection resolution and successful implant retention in 96% of patients with infected orthopedic metalwork, highlighting its effectiveness in difficult-to-treat cases.[41] Beyond general infection control, NPWT also shows promise in targeting MRSA. It was demonstrated that vacuum-assisted closure (VAC) therapy significantly inhibited MRSA biofilm formation, particularly against CC5-MRSA-SCCmec I-agrII, a globally dominant clone.[42] Furthermore, dressing changes every three days produced greater antibiofilm activity, supporting protocol optimization for clinical use.[42] To enhance its therapeutic potential, novel approaches combining NPWT with local antimicrobial delivery have been developed. The use of vancomycin-loaded calcium sulfate (VLCS) alongside NPWT promoted M2 macrophage polarization, fostering an anti-inflammatory environment and improving infection resistance in open fractures.[43]

In MRSA orthopaedic infections, procedure selection hinges on implant stability, soft-tissue status, organism susceptibility, and symptom duration. Debridement, Antibiotics, and Implant Retention (DAIR) is appropriate when the prosthesis is well fixed, no sinus tract is present, symptoms are early, and active agents are available.[34] When these criteria are not met—or in chronic infection—one- or two-stage revision should be preferred; in selected spine or complex hardware cases, debridement with staged strategies is often necessary.[35] Local antibiotic delivery (PMMA or biodegradable carriers) can be integrated across pathways to raise local concentrations against biofilm, while emerging titanium-oxide/ion-doped coatings show dual antibacterial–osteogenic potential.[37-40] Negative-pressure wound therapy (NPWT) and modified systems can assist soft-tissue control and implant retention in contaminated/open settings.[41-43] On the pharmacological side, combination regimens and agents with biofilm penetration (e.g., rifampicin-based combinations) remain central.[36] Rehabilitative management. Early but safe mobilisation should follow infection control and soft-tissue stability milestones, aiming to mitigate immobilisation-related stiffness and deconditioning.[46] MRSA infection prolongs recovery trajectories versus non-infected patients and may reduce engagement in physiotherapy; structured, phase-based protocols and multidisciplinary coordination can shorten time to functional independence.[45-48]

REHABILITATION STRATEGIES FOR MRSA ORTHOPAEDIC PATIENTS

MRSA infection poses a significant challenge in the rehabilitation of orthopedic patients. The presence of infection often necessitates prolonged hospitalization due to repeated surgical procedures, extended antibiotic therapy, and the need for strict infection control measures.[44] These prolonged inpatient stays inevitably delay the initiation of mobilization and structured physiotherapy, which are critical for preventing secondary complications after orthopedic surgery.[45]

As a consequence of immobilization and infection-related surgical interventions, patients with MRSA infections face an increased risk of musculoskeletal complications such as joint stiffness, soft tissue contractures, and muscle weakness.[46] The inflammatory process, combined with restricted movement to protect infected joints or surgical sites, further exacerbates functional decline. These impairments not only limit physical performance but also complicate the overall rehabilitation pathway, making the restoration of mobility and independence more difficult.

Compared to non-infected orthopedic patients, recovery timelines are considerably longer in those affected by MRSA.[47] Delays in wound healing, repeated debridement procedures, and the psychological burden of infection contribute to slower functional gains and extended rehabilitation programs. Ultimately, MRSA infection not only compromises surgical outcomes but also significantly impairs the speed and effectiveness of physical recovery, underscoring the importance of tailored rehabilitation strategies for this vulnerable patient population.[46]

QUALITY OF LIFE OF ORTHOPAEDIC PATIENTS WITH MRSA INFECTION

Prolonged treatment regimens, repeated surgical interventions, and uncertainty about the outcome contribute to

heightened levels of anxiety and depression. The fear of reinfection or treatment failure can further intensify stress, reducing motivation and adherence to rehabilitation programs. In addition, repeated hospitalizations and the need for strict isolation precautions may lead to feelings of loneliness, social withdrawal, and diminished self-esteem. These psychological burdens not only affect mental health but can also directly hinder functional recovery, as emotional distress often translates into reduced engagement in physiotherapy and rehabilitation efforts.

Beyond the physical and emotional impact, MRSA infection imposes a considerable socioeconomic strain on both patients and healthcare systems. Extended hospitalization, multiple surgeries, and prolonged courses of antibiotic therapy result in substantial financial costs, often exacerbated by loss of income due to prolonged disability.[48] Family caregivers may face additional emotional and financial pressures as they provide ongoing support during recovery, which can disrupt household dynamics and quality of life.[48]

CLINICAL IMPLICATIONS FOR ORTHOPEDIC SURGEONS

Preoperative screening/decolonization reduces SSI/PJI and should be targeted to high-risk procedures and carriers.[49,50] Risk-based prophylaxis uses cefazolin routinely; add/replace with vancomycin for documented carriers/history of MRSA or high-prevalence institutions, noting risks and avoiding universal use.[50-52] Intraoperative strategy includes early, aggressive debridement; consider DAIR when prosthesis is well-fixed, no sinus tract, susceptible organisms, and adequate soft tissue.[34] Diagnostics: negative MRSA PCR (nasal/wound) supports de-escalation of empiric anti-MRSA therapy, improving stewardship without compromising outcomes.[28-32] In addition, select local antibiotic delivery (e.g., PMMA/calcium sulfate) in high-risk or established biofilm settings and NPWT (including modified or irrigating systems) to aid infection control and retention.[37-43] Antibiotic choice may consider evidence for linezolid/tedizolid or minocycline+rifampicin in specific MRSA scenarios.[54] These measures convert microbiologic insights into day-to-day surgical pathways and protocols.

PREVENTION AND CONTROL MEASURES

The prevention of MRSA infections in orthopaedic surgery requires an integrated strategy spanning preoperative, intraoperative, and postoperative phases. Recent evidence and expert consensus emphasize the importance of combining screening and decolonization, risk-based prophylaxis, strict infection control measures, and antimicrobial stewardship to limit MRSA-related SSIs and PJIs.

MRSA nasal carriage is an established risk factor for SSIs and PJIs. Routine screening with nasal swabs, followed by decolonization using mupirocin ointment and chlorhexidine baths, has demonstrated significant reductions in infection rates in orthopaedic surgery.[49] Targeted decolonization is especially important for high-risk patients, such as those undergoing prosthetic joint implantation, and in areas with moderate to high MRSA prevalence.[50] Conversely, in low-prevalence settings, selective screening of high-risk patients may be more cost-effective.[14]

Antibiotic prophylaxis remains essential to preventing MRSA SSIs. International guidelines and consensus statements recommend cefazolin for standard prophylaxis, reserving vancomycin (alone or in combination) for patients with documented MRSA colonization, history of MRSA infection, or in hospitals with high MRSA prevalence.[50] A recent multicenter study confirmed that vancomycin prophylaxis is associated with lower MRSA SSI risk in carriers, but universal prophylaxis is not recommended due to risks of nephrotoxicity, infusion reactions, and antimicrobial resistance.[51] Institutional antimicrobial policies should therefore tailor prophylaxis based on both patient risk and local resistance epidemiology.[52]

Robust infection prevention programs are critical to reducing nosocomial MRSA transmission. Righi et al. emphasize that adherence to basic infection control measures—including hand hygiene, contact precautions, and isolation of MRSA-positive patients—remains the foundation of prevention.[50] In orthopaedic practice, bundled approaches integrating preoperative screening, skin antisepsis, perioperative normothermia, and intraoperative sterile technique have been shown to significantly lower SSI rates.[49] Continuous surveillance and audit-feedback loops are necessary to maintain compliance and effectiveness.

Antimicrobial stewardship programs (ASPs) are indispensable in reducing unnecessary use of anti-MRSA agents and minimizing resistance pressure. The need for protocolized prophylaxis duration, early de-escalation when cultures exclude MRSA, and avoidance of prolonged empirical anti-MRSA therapy are important.[50] Recent reviews and cohort studies demonstrate that stewardship interventions, such as prospective audit and feedback, vancomycin restriction, and MRSA PCR–guided de-escalation, reduce linezolid and vancomycin consumption while maintaining clinical outcomes.[53]

EMERGING APPROACHES AND FUTURE DIRECTIONS

Despite ongoing challenges, multiple innovative strategies are under investigation to address MRSA infections in orthopaedics. These approaches span drug discovery, biological therapies, biomaterials, and precision diagnostics, reflecting the need for multidisciplinary solutions.

The development of new antimicrobials remains central to combating MRSA, particularly in orthopaedic infections where biofilms reduce the efficacy of conventional therapy. A recent network meta-analysis confirmed that linezolid, combined with minocycline and rifampicin, and tedizolid offer superior or comparable efficacy compared to vancomycin.[54] However, the WHO pipeline review revealed a lack of genuinely novel antibiotic classes entering late-stage trials, with most candidates being derivatives of existing drugs.[55] This highlights an urgent innovation gap and the risk of future resistance even to newer agents.

Bacteriophage therapy has gained attention as a promising adjunct in the management of antibiotic-resistant strains, especially PJIs. A recent systematic review of clinical reports highlighted

encouraging outcomes, with phage therapy used alongside debridement and systemic antibiotics leading to infection resolution in many refractory cases.[56] Bacteriophages control bacterial infection primarily through receptor binding, genome injection, and replication via the lytic cycle, leading to host cell lysis, or the lysogenic cycle, with potential later induction of lysis.[56] Beyond direct killing, phages degrade biofilms, reduce bacterial virulence, enhance immune clearance, and may disrupt dormancy-based defenses through effects on sporulation.[56] Clinically, phage therapy has shown high efficacy with mostly mild, self-limiting adverse reactions, underscoring its promise as an adjunct in infection management. Beyond natural phages, innovative approaches are under development. CRISPR-Cas–engineered phages are being designed to disrupt resistance genes, restoring susceptibility to conventional antibiotics selectively.[57] Preclinical work has also shown synergistic effects when phages are combined with antibiotics, lowering bacterial burden more effectively than either therapy alone. Despite these advances, significant challenges remain, including regulatory approval, standardized dosing regimens, and large-scale clinical validation.

Immunotherapeutic strategies against biofilm-associated S. aureus infections enhance host defense while reducing antibiotic reliance. Monoclonal antibodies (e.g., TRL1068, F598) neutralize adhesins and resist immune evasion, while vaccines such as 4C-Staph and Sta-V5 elicit strong Th1/Th17 responses. Passive immunization with anti-PBP2a IgG and novel platforms, including extracellular vesicle–based and conjugate vaccines, further reduces bacterial burden and disrupts biofilm formation. Targeting wall teichoic acid or dPNAG has also shown significant bacteremia reduction in preclinical models.[24] Clinical translation, however, remains distant, with no licensed vaccines currently available.

Recent advances in implant surface engineering and nanotechnology aim to overcome the persistent challenge of implant-associated infections by combining antibacterial efficacy with osteointegration. Nanostructured coatings, such as silver, zinc oxide, and titanium dioxide nanoparticles, provide sustained antimicrobial activity through ion release, reactive oxygen species generation, and biofilm disruption while maintaining biocompatibility.[58] Multifunctional polymeric and bioactive coatings further enable localized antibiotic delivery and synergistic antibacterial effects, reducing systemic toxicity. In addition, surface modifications using nanotopographies or functionalized biomolecules can prevent bacterial adhesion while promoting osteoblast attachment, thereby enhancing implant integration.[58] These strategies highlight the promise of nanotechnology-driven implant coatings in reducing infection risk and improving clinical outcomes in orthopaedic surgery. Although these technologies are promising in vitro and in vivo preclinical settings, clinical evidence remains scarce, and questions about long-term safety, cost-effectiveness, and regulatory approval need resolution.

Emerging diagnostic platforms are enabling more tailored approaches to MRSA management. Rapid PCR assays and next-generation sequencing (NGS) allow earlier pathogen identification and resistance profiling, particularly in culture-negative PJIs.[59,60] Additionally, biofilm susceptibility testing by measuring the minimal biofilm eradication concentration (MBEC) has been proposed to guide implant-retention decisions and optimize antimicrobial therapy.[60] These strategies align with the vision of precision medicine in orthopaedic infections, where diagnostics inform individualized surgical and pharmacological decisions. Standardization, cost, and integration into routine care, however, remain obstacles before widespread clinical adoption.

CONCLUSION

MRSA continues to pose a substantial challenge in orthopaedic practice, fueling surgical-site and prosthetic joint infections as well as osteomyelitis, with significant morbidity and economic impact. Its pathogenic success, driven by biofilm formation, evasion of host defenses, and broad antimicrobial resistance, complicates timely diagnosis and definitive clearance, particularly when implants are involved. Although targeted screening, tailored perioperative prophylaxis, and antimicrobial stewardship have lowered infection rates, important gaps remain, notably in resource-limited settings. Therapeutic choices are further narrowed by escalating resistance to glycopeptides and other last-line agents, while biofilm resilience frequently forces complex revision procedures. Innovations such as next-generation antimicrobials, bacteriophage-based approaches, immunotherapeutics, nanocoated implants, and individualized diagnostic platforms are encouraging but confined mainly to preclinical or early clinical evaluation. Meaningful progress will require coordinated, multidisciplinary care. International partnership, fair access to diagnostics and treatments, and sustained research investment are essential to translate emerging advances into routine orthopaedic practice and lessen the overall burden of MRSA.

ETHICS CONSIDERATION

This article is a narrative literature review that does not involve new human or animal participants, identifiable personal data, or interventional procedures. Therefore, ethical approval and informed consent were not required. All data were obtained from previously published studies that state their own ethical assurances.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest related to the content of this manuscript.

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AUTHOR CONTRIBUTIONS

YH, RMY, and SAK jointly conceived the study aims and overall framework. RMY designed the review strategy and inclusion–exclusion criteria, led the literature search, article screening, data extraction, and synthesis, and drafted the initial manuscript. YH, MPJ, MAU, and MS provided methodological guidance,

assessed the coherence of the evidence and argumentation, and undertook substantive revisions to the background, pathogenesis, and clinical implications. SAK, JA, ARS, and YDP contributed to data curation (tabulating key findings and study summaries), verification of citations/references, preparation of supporting figures/tables, and technical editing. All authors contributed to data interpretation, critically reviewed the full manuscript, approved the final version, and accept responsibility for the integrity and accuracy of the work.

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