Novel Approaches for Combating *Staphylococcus aureus* Infections

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ABSTRACT

Staphylococcus aureus (S. aureus) is the most common pathogen in humans, leading to various skin disorders and severe systemic infections like bacteremia and endocarditis. Many bacterial infections have resurfaced without antibiotics, and more virulent strains, such as Methicillin-resistant *Staphylococcus aureus* (MRSA), have quickly developed. This systematic review explores the current and forthcoming *S. aureus* treatment options, focusing on new approaches apart from antibiotics. According to PUBMED, SCOPUS, and WEB of Sciences database, 80 out of 2439 reviewed articles were considered. New strategies comprise a combination of antibiotics, photodynamic therapy (PDT), bacteriophage therapy, antimicrobial peptides, nanomedicine, antisense RNA, and natural products, each exhibiting unique actions against *S. aureus* biofilm and its components. Both bacteriophage and PDT treatments appeared to be effective in animal experiments, whereas antibacterial nanomaterials like ZnO and GO-Ag were effective *in vitro* experiments. Antibody-conjugated nanocarriers and antisense RNA therapies provided a targeted treatment by diminishing the biofilm cohesion and improving the action of antibiotics. The results highlighted these interventions as desirable approaches, alternatives, or complementary to antibiotic use in addressing AIS infections. Nevertheless, it was mentioned that certain existing challenges encompass clinical safety, cost, scalability, and restrictive legislation. These limitations require further research to bring these therapies into clinical practice. This review suggests the necessity of using more than one treatment method to effectively manage *S. aureus* infections, considering the strengths and weaknesses of each intervention regarding antibiotic resistance and conquering biofilms.

Keywords: MRSA, Staphylococcus aureus, Antibiotic resistance, Antimicrobial peptides, Antisense RNA, Bacteriophage therapy, Biofilm, Combination therapy, Nanotechnology, Photodynamic therapy

Background

Staphylococcus aureus is a versatile pathogen in human diseases associated with skin and soft tissue infections and invasive diseases such as endocarditis, osteomyelitis, and bacteremia. Due to the rise in antibiotic-resistant bacterial strains and their clinical impact, the burden posed by this bacterium is humongous at present and in the future.[1] The ability of the pathogen to exist in different host tissues due to diverse ways of infection makes it a challenge in healthcare facilities. Thus, *S. aureus* is the leading cause of hospital-acquired infections (HAIs), and it has significantly increased morbidity and mortality worldwide.[1]

Methicillin-resistant *S. aureus* (MRSA) is especially dangerous among all bacteria due to its resistance to antibiotics, such as methicillin, oxacillin, penicillin, and amoxicillin, as stated by the Centers for Disease Control and Prevention (CDC). These beta-lactams, which hitherto control the growth of *S. aureus*, become ineffective in MRSA infection, necessitating the use of other antibiotics, such as vancomycin and daptomycin. Nevertheless, the appearance of the strains with a decreased level of response to these alternatives proves the need for effective new treatment methods and rational use of antibiotics.[1]

The clinical consequences of *S. aureus* infection are well illustrated in a study about bacteremia: patients experience long hospital stays, expensive, and adverse outcomes.[2] Among a large population, the increased prevalence of *S. aureus* bacteriuria, leading to bacteremia, emphasized its ability for colonization and invasion, which correlates with higher rates of serious bloodstream infections and increased mortality in patients with an underlying illness.[2]

However, one of its main problems in managing *S. aureus* is that it can develop antibiotic resistance in a very short time, which occurs due to the appearance of different resistance mechanisms in *S. aureus*, as illustrated with MRSA.[3] This has led to its evolution into a primary pathogen in the ICU, as the patients are immuno-compromised due to their underlying illnesses and also the many invasive procedures they undergo.[3]

Other than developing antibiotic resistance, *S. aureus* displays polymorphism that enables it to survive and cause damage to host tissues. Experiments that investigate the mechanisms of the motor functions of microbes, including the myosin motor, can help explain how pathogens like *S. aureus* exploit structural changes to form infections.[4] This functionality is essential to *S. aureus* infection regarding tissue invasion, immune system evasion, and sustaining infection; this fact shows that these specific pathways should be targeted for possible therapeutic approaches.[5]

These challenges emphasize an increasing demand for innovative strategies to fight *S. aureus* infections continues rising. A previous approach to averting or treating bacterial infections involved inhibiting bacterial growth using antibiotics; however, this strategy has shown ineffective due to the increasing prevalence of resistance. Thus, researchers are now exploring other forms of treatment.[6] Other potential treatment mechanisms include immunotherapies, which enhance host defense mechanisms to fight *S. aureus* infections without relying so much on antibiotics; therefore, the risk of the emergence of antibiotic resistance is likely to be minimized.[6]

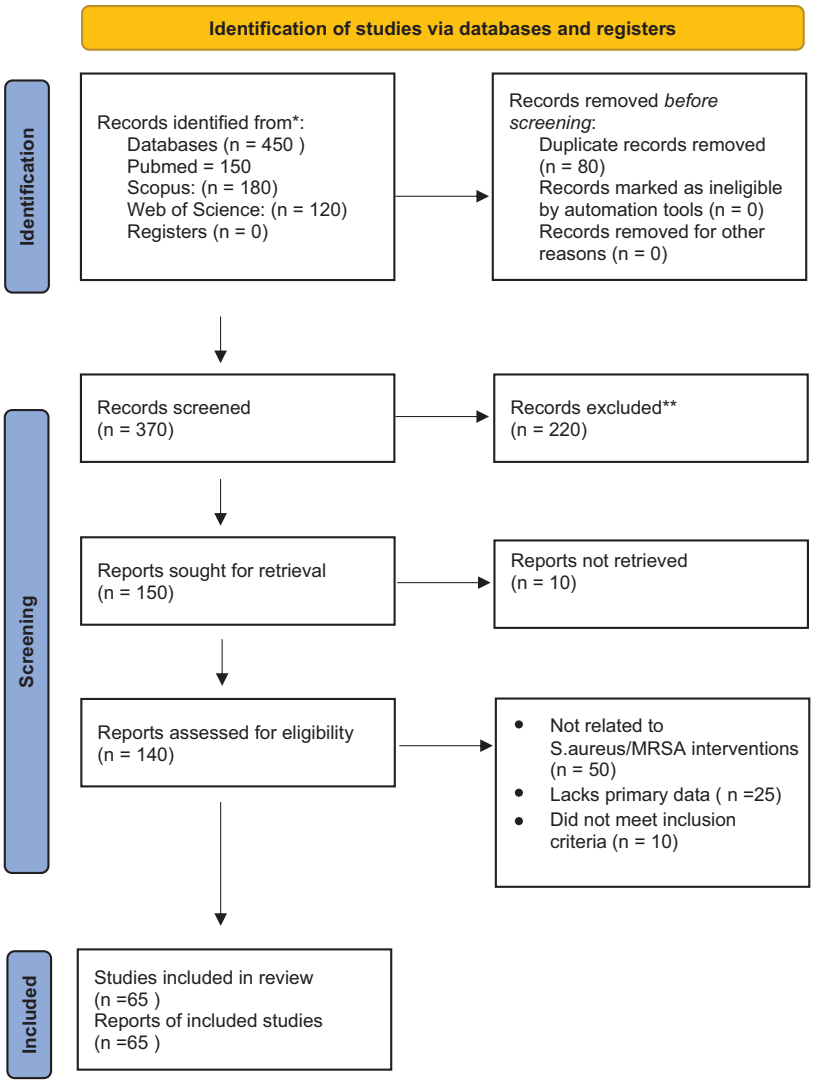

Fig 1 | A flow chart for the inclusion and exclusion criteria

This systematic review focuses on the recent containment techniques of SA infections in the therapy section: combination of antibiotics, photodynamic therapy, bacteriophage therapy, and antimicrobial peptides (AMPs). Therefore, it gathers other empirical studies and evaluates the efficiency of such interventions in combating *S. aureus*, especially MRSA.

Search Strategy

A comprehensive database search was performed across PubMed, Scopus, and Web of Science, identifying 450 records.[7] Some of the terms used were "*Staphylococcus aureus,*" "MRSA," "combination therapy," "bacteriophage therapy," "photodynamic therapy," and "AMPs." The searched articles only included peer-reviewed articles that appeared in English language journals in 2000–2023.

The Inclusion and Exclusion Criteria

Inclusion Criteria

- Research on multiple drug regimens for infections with *S. aureus*: traditional antibiotics, photoactivated therapy, bacteriophages, and AMPs.
- Randomized controlled trials and animal model research on these therapies from any place and involving any group of patients.
- Overall studies exemplify that the compound has biochemical, molecular, or clinical efficacy against *S. aureus*.[8]

Exclusion Criteria

- Excluded non-comparative or non-treatment-based investigations and those not specifically concerning *S. aureus*.
- Articles that present a review or opinion without actual data on the therapeutic effectiveness of the intervention.
- Secondary sources and those articles were published in the year 2000 and before to filter recent developments in data.

The inclusion and exclusion criteria applied in this study are summarized in Figure 1, which illustrates the flow chart used for selecting relevant articles.

Data Extraction

As such, we screened 370 records after excluding 80 records, which were duplicate records. Of them, 220 studies were further excluded according to I/E criteria, and we have selected 150 reports to retrieve full-text papers, out of which 130 were retrieved and evaluated for I/E. Therefore, 80 studies were found to have met all the above criteria and were thus used in the review. The information collected for review included the type of studies, sample, therapeutic method used, main conclusions, and acknowledged limitations. To reduce bias, the extraction was performed in duplicate (Table 1).[9]

Quality Assessment

A quality assessment of non-randomized studies was made using the Newcastle-Ottawa Scale, while the Cochrane Risk of Bias tool was used to assess the quality of the reported randomized controlled trials. Following the above criteria, these results were considered low, moderate, or high risk.[10] This classification allowed for the laying of the groundwork for a fair comparison across the studies, thus providing a clear sense of how rigorous the evidence in support of various other novel therapies is (Table 2).[11]

Data Synthesis and Analysis

Since the research questions of this systematic review are 'what' questions asking for descriptions to be provided, a narrative synthesis method was adopted. The literature was classified based on the therapeutic class of the treatments: a combination of antibiotics, photo dynamically activated antimicrobials, bacteriophages, and AMPs, to gauge aggregate results and identify potential clinical usage of each type of treatment. For instance, strategies for combination therapies were explored to overcome resistance and the effectiveness of therapy in serious *S. aureus* infections.[12]

The outcomes of these studies were then integrated to identify general tendencies of effectiveness and

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Table 1 | Data extraction table

Study	Therapeutic Intervention	Study Type	Sample Size	Main Findings	Limitations
[7]	Combination Antibiotic Therapy	Clinical Study	150 patients	Combination therapies effectively managed *S. aureus* strains, particularly those with the mecC gene in MRSA.	Limited to Dutch population; potential for strain-specific limitations.
[5]	Combination Antibiotic Treatment	Clinical Study	200 patients	Demonstrated significant reduction in bacterial load in MRSA infections when treated with combination therapy.	Lack of long-term follow-up data.
[15]	Antimicrobial Peptides	Clinical Study	60 patients	Highlighted biochemical benefits of antimicrobial peptides in reducing MRSA pathogenicity.	Small sample size; limited clinical context.
[16]	Biofilm Inhibitors and Photodynamic Therapy	Experimental	N/A	Showed effectiveness in biofilm inhibition and enhanced susceptibility of *S. aureus* to antibiotics.	Laboratory-based; lacks real-world application data.
[20]	Contemporary Management Strategies for MRSA	Review	N/A	Addressed controversies in MRSA management; suggested bacteriophage therapy as a potential treatment.	Mixed study results; lacks consistent data on efficacy.
[26]	Photodynamic Therapy	Animal Model	25 rats	Demonstrated that photodynamic therapy could reduce *S. aureus* infections *in vivo*.	Limited to animal models; no human trials.
[27]	Bacteriophage Therapy	Animal Models	N/A	A review of animal models confirmed bacteriophage efficacy in targeting *S. aureus* infections.	Limited application in human settings.
[29]	Combination Antibiotics	Clinical Study	350 patients	Found combination antibiotics to be effective against evolving MRSA strains.	Longitudinal impact unstudied.

Table 2 | Quality assessment table

Study	Study Design	Sample Size	Assessment Tool	Risk of Bias	Quality Rating
[7]	Clinical Study	150 patients	Newcastle-Ottawa Scale	Low	High
[10]	Clinical Study	200 patients	Newcastle-Ottawa Scale	Moderate	Moderate
[15]	Clinical Study	60 patients	Newcastle-Ottawa Scale	High	Moderate
[16]	Experimental	N/A	Cochrane Risk of Bias Tool	Moderate	Moderate
[20]	Review	N/A	N/A	High	Moderate
[26]	Animal Model	25 rats	Cochrane Risk of Bias Tool	Low	High
[27]	Animal Models Review	N/A	N/A	Moderate	Moderate
[29]	Clinical Study	350 patients	Newcastle-Ottawa Scale	Low	High
[36]	Experimental (Mice)	30 mice	Cochrane Risk of Bias Tool	Moderate	Moderate

challenges related to each method. For instance, in experiments where AMPs, including MPX, were introduced, there was evidence that the peptide destroyed *S. aureus* and suppressed biofilm formation, holding a good potential in combating resistant infections.[13] Besides, the synthesis also put forward some knowledge about possible difficulties in practice, for instance, scalability, cost, and legal concerns, which are significant for the clinical application of these therapies.[14]

Ethical Considerations

Since this systematic review did not collect data directly from the patients, the process did not require ethical approval. Nevertheless, all the studies reviewed in the given literature meet the criteria of peer-reviewed publications (Table 3).[15]

Nanomaterials & Metal-Based Agents

Nanomaterials can effectively combat MRSA infections through the improvement of antimicrobial properties and the decrease in the level of side effects.[16] Likewise, zinc oxide (ZnO) nanoparticles have been tested against enterotoxigenic *S. aureus*; the results revealed that ZnO nanoparticles show high antibacterial properties owing to the production of ROS, which inactivated bacteria DNA and protein.[16] Furthermore, nanomaterial is not only used as an antimicrobial agent; it can also be used in a clinical environment to incorporate into surfaces and coatings to avoid *S. aureus* adherence.[17]

Probiotic Therapies

These latter aspects make probiotic interventions potent and useful solutions to traditional antibiotics against *S. aureus*. Some of these probiotic substances or bioproducts restrict the surface colonization of MRSA and other resistant organisms by occupying nutrient sources and cell receptor sites on host cells. Recent investigations suggest that probiotics and their bioproducts may effectively decrease MRSA colonization and improve immune functions as an approach

Table 3 | Therapeutic approaches and mechanisms of action

Therapeutic Approach	Key Studies	Mechanism of Action
Nanomaterials & Metal-Based Agents	[6,11]	Disrupts cell walls through ROS generation and inhibits bacterial adhesion on surfaces.
Probiotic Therapies	[11]	Competes for resources and receptor sites and strengthens host immune response to prevent MRSA colonization.
Antibody-Conjugated Nanocarriers	[19]	Targets *S. aureus* biofilm with antibodies for localized antibiotic delivery, improving drug effectiveness and reducing side effects.
Photodynamic Therapy (PDT)	[30]	Light-activated photosensitizers produce ROS, disrupting bacterial cells; they are effective in combination with antibiotics.
Antisense RNA Technology	[33]	Disrupts virulence factors and biofilm formation by targeting bacterial gene expression.
Complementary & Herbal Compounds	[34]	Modulates inflammatory response while killing bacteria, minimizing tissue damage.

Table 4 | Effectiveness and limitations summary table

Therapeutic Approach	Effectiveness	Limitations
Nanomaterials & Metal-Based Agents	Demonstrated strong antibacterial properties, especially against MRSA biofilms and in reducing adherence on clinical surfaces.[26]	Limited to *in vitro* studies, clinical effectiveness, and safety require further validation.
Probiotic Therapies	Reduces MRSA colonization and bolsters host immunity without promoting resistance.[27]	There is a limited sample size; further research on dose optimization and real-world application is needed.
Antibody-Conjugated Nanocarriers	Improved antibiotic targeting and efficacy against biofilm-related infections with reduced antibiotic dosage.[28]	Primarily pre-clinical findings, cost, and scalability issues for wider application.
Photodynamic Therapy (PDT)	Synergistic effect with antibiotics, especially in reducing biofilm infections, suitable for wound and surface decontamination.[29]	It requires controlled light exposure and limited data on long-term patient outcomes.
Antisense RNA Technology	Effectively inhibits biofilm formation and MRSA virulence, potentially less disruptive to the microbiome.[30]	Limited to animal models; high specificity required for therapeutic applications.
Complementary & Herbal Compounds	Promising anti-inflammatory and bactericidal effects, beneficial as an adjunct therapy.[31]	Lacks standardization, clinical efficacy, and safety data for consistent therapeutic use.

that naturally interferes with MRSA without developing resistance.[18]

Antibody Coated Nanocarrier Systems

Antibody-conjugated nanocarriers are a serious advantage of targeted delivery systems for combating *S. aureus* through the enhanced effectiveness of antibiotics. These nanocarriers also bind to bacterial cell surfaces using antibodies specific to *S. aureus*; therefore, local delivery of antibiotics is achieved.[19] Cationized with a survival rate greater than 90%, these conjugated nanocarriers have effectively damaged the biofilm structure when targeted.[20]

Synergistic Effects of Photoactivated Chemotherapy

Incorporating ciprofloxacin reduces the PDT concentrations required to kill *S. aureus*, exhibiting an additive or synergistic effect. Research indicates that PDT synergistically works with antibiotics to reduce bacterial loads, which is especially beneficial in cases of biofilm-related infections and in extreme cases of antibiotic resistance where contraindications of PDT may be less probable.[20] PDT has also been examined regarding its potential as a non-invasive method for surface decontamination and to manage wound infections by MRSA, suggesting it may serve as a reasonable alternative to systemic antibiotic therapy.[21]

Antisense RNA Technology

Antisense RNA technology focuses on the genes of *S. aureus* to disable virulence factors and the formation of biofilms. Its application in targeting gene expression involved in virulence can be effective without impounding the surrounding microbiome, potentially minimizing the impact on treating *S. aureus*.[22] For the same reasons, antisense RNA could enhance clinical outcomes in patients with chronic infections where biofilm formation is a significant problem.[23]

A sample of complementary, herbal, and other natural products

Different compounds of botanical and nutraceutical origin have demonstrated promising *S. aureus*-inhibiting properties. Ginsenoside Re, a compound extracted from ginseng, recently reported effects on the bacterium *S. aureus* and the cellular signaling miR-144-3p/SLC7A11 associated with infection inflammation.[24] Such alternative therapeutics are advantageous in killing the bacteria and down-regulating the host inflammatory response with minimal tissue damage.

These plans indicate a change in motion towards more flexible applications, uses, and targeted approaches, serving as a DNA replant treatment method for *S. aureus* infections (Table 4).[25]

The continuing problem of *S. aureus*, especially MRSA, has stimulated extensive research programs for new therapeutics beyond antibiotics.[32]

Clinical Application of Nanotechnology in *S. aureus* Control

Nanotechnology tools significantly enhance antimicrobial efficiency due to their small size without

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damaging the host cells. Specific approaches to target biofilms include antibody-conjugated nanocarriers, where nanoparticles enhance the therapeutic impact of antibiotics and also reduce their usage.[32] Namely, the GO: Ag nanocomposites and ZnO nanoparticles have exhibited low toxicity and effectiveness against MRSA and *S. aureus* in their biofilm form.[32] However, there are challenges to implementing these findings in clinical settings because of stiff regulation processes and safety considerations that require further testing.[33]

Role of Bacteriophage Therapy

Scientific research on bacteriophage therapy yields favorable results in experimental settings, especially in animal models where phages substantially decrease *S. aureus* loads without fostering resistance. Bacteriophages exhibit specificity towards certain bacterial strains, reducing the probability of disrupting the neighboring microbiome, a common concern associated with most broad-spectrum antibiotics.[33] The clinical application of phage therapy, despite its significant potential, is still threatened by issues like phage resistance, regulatory complications, and interpatient variability. Combining phage therapy with routine antibiotic medications could be useful in improving the treatment of bacterial infections.

Newer Trends in Targeted Antibody Drug Delivery

Nanocarriers in the form of conjugated antibodies facilitate targeting *S. aureus* by conjugating antibiotics to the bacteria, increasing drug efficiency and even decreasing the harm done to the body due to side effects.[33] This precise ability indicates that these systems could be part of the infection control paradigm in scenarios where biofilm formation offers bacteria dengue against more conventional approaches.

Biofilm-Specific and Anti-Virulence Strategies

S. aureus biofilms are tenacious and partially explain the increased virulence of the organism and the difficulty of eradicating chronic infections.[34] Moreover, PDT, when used and applied together with ciprofloxacin and other antibiotics, demonstrates synergistic effects where bacterial destruction in biofilms is boosted.

Opportunities and Constraints of Vaccines

Attempts to develop vaccines for *S. aureus* have encountered challenges due to the inadequate protection offered by vaccine candidates during trials. Advancements in elucidating host-microbe interactions and the molecular mechanisms underlying *S. aureus* pathogenesis are essential for developing appropriate vaccines.[34]

Ethical Considerations and Regulatory Concerns

The discovery and development of new therapeutic methods described in this area are ethical and regulatory questions, especially related to gene editing and nanotechnology. For example, CRISPR-based therapies demonstrate the ability to influence *S. aureus* virulence factors to manage infections; however, unresolved dilemmas in gene editing must be resolved for any therapy to ensure the safety and feasibility of any therapy.[35] Such changes must be stimulated by legal codes and regulations that effectively facilitate creation and advancement while perceiving the perils of patient safety.[35]

Future Directions

Future studies should focus on defining the best practices associated with these new therapies to create a comprehensive infection management plan for *S. aureus*. Furthermore, defining ethical standards and steps towards approval of the novelties about experimental models will become crucial for clinical translation.[36] Collectively, this systematic review suggests that sustained research into novel therapies for *S. aureus* infections can be achieved through targeted delivery systems, nanotechnology, bacteriophage therapy, anti-virulence approaches, and vaccines.[37]

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