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Staphylococcus haemolyticus: Tackling Multidrug Resistance and Biofilm Hurdles–Advances in Antimicrobial Strategies: A Review Study

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ABSTRACT

Background: *Staphylococcus haemolyticus*, an emerging coagulase-negative staphylococcus (CoNS), drives hospital-acquired infections (HAIs) in immunocompromised patients and those with indwelling devices, fueled by its multidrug resistance (MDR) and robust biofilm formation. Despite its clinical significance, *S. haemolyticus* remains understudied compared to other staphylococci.

Materials and Methods: A systematic literature review was conducted using PubMed and Google Scholar from 2020 to 2025. Keywords included *S. haemolyticus* AND (MDR OR biofilm OR phage therapy OR 'antimicrobial peptides [AMPs]). The inclusion criteria comprised peer-reviewed articles on mechanisms, epidemiology, or therapies in humans and animals. The initial search yielded 1,247 hits; after the removal of duplicates (n=312) and title/abstract screening, 156 full texts were assessed.

Results: *S. haemolyticus* exhibits MDR primarily through mecA-mediated methicillin resistance and horizontal gene transfer (HGT). Biofilm formation enhances antibiotic tolerance and immune evasion. Key virulence factors, including surface proteins and phenol-soluble modulins, contribute significantly to its pathogenesis. Novel therapeutic approaches, such as antimicrobial peptides and bacteriophage therapy, demonstrate promising efficacy against MDR strains in preclinical studies.

Conclusion: This review highlights *S. haemolyticus* as an underestimated threat in HAIs, emphasizing the need for targeted therapies and advanced diagnostics. Future research should focus on clinical trials for novel antimicrobials, global epidemiology, and omics-driven drug discovery to combat this resilient pathogen.

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Introduction

Staphylococcus haemolyticus, a coagulase-negative staphylococcus (CoNS), is a common skin commensal that can act as an opportunistic pathogen, particularly in immunocompromised patients or those with indwelling medical devices [1, 2]. Despite lacking coagulase activity, unlike *Staphylococcus aureus*, *S. haemolyticus* is recognized as a significant opportunistic pathogen responsible for severe infections, including bacteremia, endocarditis, and prosthetic joint infections (PJIs), particularly in association with medical devices in hospital environments [3, 4]. These infections, such as bacteremia, are frequently exacerbated by the multidrug-resistant (MDR) nature of *S. haemolyticus*, with epidemiological surveillance indicating an MDR prevalence ranging from 54% to 79% among hospital-acquired isolates, particularly those recovered from neonatal intensive care units (NICUs) and burn wards [5, 6]. Case reports indicate that immunocompromised individuals, as well as those with co-infections or underlying comorbidities, face a higher risk of fatality due to *S. haemolyticus* infection [7]. A hallmark of *S. haemolyticus* is its ability to form biofilms, which is crucial for disease persistence. The exopolysaccharides produced during biofilm formation can also inhibit the growth and development of biofilms in competing bacterial species [8]. Despite its increasing clinical relevance, *S. haemolyticus* remains understudied compared to other staphylococci, particularly in terms of its molecular mechanisms of virulence and resistance. This review addresses this gap by synthesizing recent findings on *S. haemolyticus* pathogenesis, antibiotic resistance, and novel therapeutic approaches, providing a foundation for targeted research and improved clinical management.

Materials and Methods

This narrative review synthesizes recent literature on *S. haemolyticus* pathogenesis, multidrug resistance (MDR), and therapeutic strategies in human clinical infections. A systematic literature search was conducted using PubMed and Google Scholar from 2020 to 2025 to capture studies reflecting advances following research on *S. aureus* and *Staphylococcus epidermidis*. The keywords included '*Staphylococcus* haemolyticus' And 'multidrug resistance' OR 'biofilm' OR 'antimicrobial peptides (AMPs)' OR 'phage therapy' OR 'phytochemicals' OR 'hospital-acquired infections (HAIs)'.

Inclusion criteria encompassed peer-reviewed articles in English, focusing on human clinical infections, molecular mechanisms, epidemiology, or novel therapies for *S. haemolyticus*. Exclusion criteria included studies primarily on other staphylococci, non-peer-reviewed sources, or pre-2020 data unless deemed seminal. The search yielded 1,247 articles; after removing duplicates (n=312) and screening titles and abstracts, 156 full-text articles were assessed, with 60 included for qualitative synthesis. Evidence quality was evaluated based on study design (e.g. clinical trials, cohort studies, in vitro/in vivo models) and journal impact, prioritizing high-quality primary research and systematic reviews. As a narrative synthesis, this review integrates findings without meta-analytic methods, acknowledging potential biases from selective study inclusion and varying study designs. Limitations included the scarcity of *S. haemolyticus*-specific clinical trials and potential underreporting of community-acquired infections.

Components of *S. hemolyticus* Pathogenicity

Biofilm formation

Biofilm formation is a hallmark of *S. haemolyticus* pathogenicity, enabling persistent infections on indwelling medical devices, such as catheters and prosthetic joints [9]. Unlike *S. aureus* and *S. epidermidis*, *S. haemolyticus* forms biofilms independently of the ica operon, relying on autolysin E (AtlE) and surface proteins Bhp and Fbe for initial attachment to vitronectin and fibrinogen [10, 11]. Subinhibitory concentrations of cefotaxime have been shown, paradoxically, to enhance biofilm formation in coagulase-negative staphylococci, including *S. haemolyticus*, by inducing the release of extracellular DNA (eDNA), as demonstrated in in vitro investigations [12]. Vancomycin exhibits limited effectiveness against biofilms and displays poor intracellular penetration [13]. Rifampicin demonstrates strong anti-biofilm activity against *S. haemolyticus* by disrupting the biofilm matrix and decreasing bacterial viability. However, the rapid emergence of resistance mutations necessitates its use in combination therapy with agents, such as vancomycin or daptomycin to maintain therapeutic efficacy and prevent resistance development [13]. Another study revealed that fusaric acid derivatives, such as qy17, suppress *S. haemolyticus* biofilm formation by modulating the expression of genes associated with stress response and virulence, suggesting promising therapeutic potential [14].

Important surface proteins, enzymes, and toxins of *S. haemolyticus*

S. haemolyticus employs a repertoire of virulence factors to enhance its pathogenicity. Fibronectin-binding

proteins (FnBPs) facilitate adhesion to the extracellular matrix, enabling host cell invasion and tissue penetration [15]. These observations align with those reported by Eltwisy et al., indicating that *S. haemolyticus* utilizes biofilm formation and FnBPs to enhance adhesion and internalization into host cells. Once internalized, the bacterium secretes various toxins and enzymes that contribute to tissue damage, stimulate the release of proinflammatory cytokines, and ultimately lead to host cell death [16]. Additional virulence-related elements include adhesion proteins, such as elastin-binding protein (Ebp), fibrinogen-binding protein (SdrE), the immune evasion molecule capsular polysaccharide B (CapB), and the cytolytic toxin CylR2. Notably, Ebp and SdrE are involved in mediating bacterial attachment to host cells, whereas cytolysins, such as CylR2, significantly contribute to the pathogenic potential of *S. haemolyticus* [17]. In a study, Wolden et al. reported 65 surface-associated proteins in *S. haemolyticus*, with SceD and Atl showing notably increased expression during keratinocyte colonization, potentially facilitating persistent infection [18]. *S. haemolyticus* secretes enzymes and toxins that enhance its pathogenicity by degrading host immune factors and promoting inflammation [13]. Staphylococcal enterotoxins (SETs), encoded by genes, such as *sea*, *seg*, and *sei*, function as superantigens, triggering cytokine release and contributing to severe outcomes, including sepsis [19, 20].

Clinical Impact

The diseases listed in Table 1 highlight the diverse clinical impact of *S. haemolyticus*, with nosocomial infections and sepsis posing the most significant challenges due to high rates of MDR and biofilm formation [13, 21-23]. Community-acquired infections, such as urinary tract infections (UTIs), are increasingly reported, particularly in the elderly and catheterized patients [24]. Current guidelines recommend catheter removal and a 5-7 day course of antibiotics for catheter-related bloodstream infections (CRBSI) caused by CoNS, but emerging evidence supports reevaluating the necessity of antibiotics in low-risk cases [25]. These findings underscore the need for enhanced diagnostics and targeted therapies to manage *S. haemolyticus* infections effectively.

MDR Mechanisms

S. haemolyticus is a major driver of HAIs due to its MDR, affecting antibiotics, such as β-lactams, quinolones, macrolides, and aminoglycosides [28]. Resistance to methicillin, mediated by *mecA* or *mecC* genes, encodes a modified penicillin-binding protein (PBP2a), rendering β-lactam antibiotics ineffective [29]. Recent genomic research has identified new mec variants, with the ccr complex being a crucial part of the entire SCCmec cassette. This complex encodes the ccr recombinases (ccrA, ccrB, and ccrC), which facilitate the integration and excision of SCCmec from the recipient chromosome, playing a key role in its mobility [30]. Furthermore, the co-location of cfr, optrA, and vanA on linear plasmids has been observed, leading to MDR to linezolid and oxazolidinones in staphylococci [31]. These factors highlight the significance of *S. haemolyticus* as a reservoir for resistance [32].

Recent epidemiological data from 2023 to 2025 indicate a rising prevalence of MDR *S. haemolyticus* in NICUs, with clonal outbreaks of ST29/CC3 reported in France (up to 60% of isolates in preterm infants) [5, 33]. In Asia, particularly China, genomic analyses of burn wound isolates have revealed high resistance to

Table 1. Clinical diseases caused by *S. haemolyticus*

Disease	Description	At-risk Populations	Clinical Outcomes and Challenges	Ref.
Nosocomial Infections	Biofilm-mediated infections on catheters, prosthetic joints, and other devices	Immunocompromised patients, ICU patients, and neonates	Persistent infections due to MDR; high mortality in MDR cases, often requiring device removal and prolonged therapy	[13, 23, 26, 27]
Sepsis	Bloodstream infections, primarily catheter-related	Immunocompromised patients and indwelling device users	High mortality risk in neonates with MDR CoNS; requires prolonged antibiotic therapy	[13, 26]
UTIs	MDR infections of the UTI	Elderly and catheterized patients	Recurrent infections; limited effective antibiotics	[23]
PJIs	Biofilm-mediated infections on prosthetic joints	Patients with orthopedic implants	Chronic infections; may require surgical revision	[13]
Diabetic foot ulcer infections	Opportunistic infections causing tissue damage and delayed healing	Diabetic patients	Risk of osteomyelitis; potential need for amputation	[16]

Table 2. Key resistance mechanisms, associated genes, and their clinical implications

Antibiotic	Resistance Mechanism	Associated Genes	Clinical Implications	Ref.
Methicillin	Modified PBP2a reducing β-lactam affinity	*MecA* and *MecC*	Limits β-lactam use; requires vancomycin or linezolid	[29]
Glycopeptides (e.g. vancomycin, teicoplanin)	Altered cell wall precursors or regulatory gene mutations	*vanA*, *graS*, and *tcaRAB*	Reduce the efficacy of last-resort antibiotics	[37, 38]
Linezolid	23S rRNA mutations or cfr-mediated methylation	*cfr* and *23S rRNA* mutations	Restricts options for MDR strains	[31, 39]
Lincosamides (e.g. clindamycin)	Efflux or enzymatic inactivation	*lnu(A)* and $vga(A)_{LC}$	Limit the use in skin infections	[13, 40]
Mupirocin	Altered isoleucyl-tRNA synthetase	*mupA*	Impairs decolonization strategies	[41]
Tetracyclines (e.g. tigecycline)	Efflux pumps or ribosomal protection	*tet(K)* and *tet(L)*	Reduce efficacy in biofilm infections	[34]
Aminoglycosides (e.g. gentamicin)	Enzymatic modification	*aac(6')/aph(2'')*	Restrict catheter infection treatment	[34, 42]

β-lactams (95%) and emerging vancomycin-intermediate strains [6]. Globally, *S. haemolyticus* acts as a reservoir for resistance genes via horizontal gene transfer (HGT), exacerbating HAIs in immunocompromised individuals [32].

Azharollah et al. reported that clinical isolates show high resistance to erythromycin (79.6%), cefoxitin (71.4%), and ciprofloxacin, with 54.1% exhibiting MDR. Community-acquired isolates exhibit a lower prevalence of MDR (20%), but notable resistance to tigecycline (40%) [34]. Treatment of MDR *S. haemolyticus* relies on last-resort antibiotics, such as vancomycin and linezolid; however, emerging resistance, including vanA-mediated vancomycin resistance and cfr-driven linezolid non-susceptibility, poses significant challenges [35]. However, recent studies indicate that ceftobiprole and dalbavancin show high in vitro activity against *S. haemolyticus*, with 96% and 93% susceptibility, respectively [36]. These discrepancies highlight the need for standardized susceptibility testing and regional surveillance to reconcile conflicting data and guide therapy. Table 2 summarizes the key resistance mechanisms, associated genes, and their clinical implications.

Table 2 highlights the diverse resistance mechanisms of *S. haemolyticus*, with mecA-mediated methicillin resistance and vanA-driven glycopeptide resistance posing the GREATEST therapeutic challenges. Emerging resistance to linezolid and mupirocin further complicates decolonization and treatment strategies, emphasizing the need for novel antibiotics and infection control measures.

Emerging Therapeutic Strategies

Infection control and prevention

Effective infection control strategies, including restricted antimicrobial usage, enhanced hygiene protocols, and rigorous environmental cleaning, play a critical role in limiting *S. haemolyticus* transmission. Additionally, antibiofilm compounds can be applied to surfaces to enhance disinfection by eliminating preformed biofilms [43]. Topical decolonization methods, including nasal application of mupirocin and body washes with 4% chlorhexidine, have demonstrated temporary effectiveness in eliminating *Staphylococcus* carriage from the skin and nares [44].

Novel therapies

Phytochemicals also show promise; for instance, plant-derived extracts, such as Ficus carica latex and ethanol extracts of *Pimpinella anisum*, disrupt *S. haemolyticus* biofilms and exhibit notable antibacterial activity [45, 46]. However, phytochemical compounds, have been shown to enhance wound healing in diabetic mice infected with *S. haemolyticus*, exhibiting approximately 80% inhibition of bacterial growth [46].

Essential oils from *Lavandula angustifolia* and marine-derived xanthones from *Streptomyces caelestis* exhibit anti-biofilm and bactericidal effects against MDR *S. haemolyticus* [47-50]. Phage therapy disrupts *S. haemolyticus* biofilms using lytic phages, offering an alternative to antibiotics [51]. Recent studies have shown that phages initially identified against *Staphylococcus xylosus* are highly versatile and effectively target *S. haemo-*

lyticus and other significant pathogens of the same genus [52]. Recent advancements in phage therapy include the use of lytic phages that specifically target *S. haemolyticus* biofilms. In vivo studies conducted in murine wound models have demonstrated the efficacy of this approach, resulting in a reduction of bacterial loads exceeding 90% [53].

AMPs represent an emerging treatment modality for *S. haemolyticus*. Although the precise mechanism of action remains elusive, these peptides interact with various components of the bacterial envelope, disrupting their organization and facilitating the efflux of cellular contents [54]. AMPs, including engineered bacteriocins, such as romsacin, target the membranes and biofilms of MDR *S. haemolyticus* [55, 56]. In addition, romsacin shows potent activity against MDR strains, with promising in vivo data in skin infection models [57].

Gaps, Challenges, and Future Directions

Despite notable advances in elucidating the pathogenic mechanisms of *S. haemolyticus*, there remain substantial knowledge gaps. Clinical trials specifically addressing *S. haemolyticus* infections are limited, restricting the establishment of evidence-based therapeutic guidelines, particularly for MDR strains [58]. Epidemiological data on CA-infections are also scarce, as most available studies primarily focus on HAIs, especially in NICUs and ICUs [59]. Furthermore, the lack of systematic comparative analyses between *S. haemolyticus* and other CoNS with respect to virulence determinants and antimicrobial resistance mechanisms impedes the development of species-specific therapeutic approaches [58].

Diagnostic accuracy is further hindered by the phenotypic similarities among CoNS species, underscoring the need for advanced molecular and proteomic diagnostic methods. *S. haemolyticus* exhibits unique biofilm formation mechanisms (e.g. ica-independent pathways via AtlE) compared with *S. epidermidis*. However, systematic comparisons of virulence factors, resistance profiles, and therapeutic responses across different CoNS species are lacking. Comparative studies could elucidate why *S. haemolyticus* is an underestimated opportunistic pathogen. Future research should focus on identifying novel resistance determinants through integrative genomics and transcriptomics to facilitate the design of targeted antimicrobial strategies. Additionally, reinforcing infection control practices in healthcare settings is essential to limit the spread of MDR *S. haemolyticus*. Although the complete eradication of *S. haemolyticus* may not be feasible, implementing comprehensive preventive measures, such as rapid and accurate diagnostics, strengthened infection control protocols, strict environmental regulations, and the development of alternative therapies, such as bacteriophage treatment or AMPs, can significantly reduce its impact.

Conclusion

S. haemolyticus poses a growing threat in human clinical infections due to its MDR and robust biofilm formation, complicating the treatment of HAIs. This narrative review underscores the urgent need for prudent antimicrobial use, enhanced infection control, and development of novel therapies, like phage therapy and AMPs. Addressing research gaps through clinical trials, global surveillance, and omics-driven approaches will be critical in combating this underestimated pathogen.

Ethical Considerations

Compliance with ethical guidelines

This article is a review study with no human or animal sample.

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Authors contribution's

Conceptualization, methodology, resources, formal analysis, validation, visualization, project administration, and writing: All authors; Investigation: Mohammad Karimbakhsh and Mehrdad Gholami; Data curation: Mohammad Karimbakhsh and Mehrnaz Eramian; Investigation: Mohammad Karimbakhsh.

Conflict of interest

The authors declared no conflict of interest.

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