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Emerging challenges in innate immunity: *Staphylococcus aureus* and healthcare-associated infection

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ABSTRACT

Staphylococcus aureus, a prominent human pathogen, exhibits a remarkable ability to interact with host proteins involved in crucial physiological pathways, such as the complement system, coagulation cascade, and fibrinolysis cascade. This paper explores the ability of this notable bacteria to successfully manipulate and evade the host innate system, expatiating on the strategies that enhance its pathogenicity leading to implications on the healthcare system such as the propagation of diverse nosocomial infections. The investigation focuses on key *S. aureus* proteins, including Coagulase (Coa), von Willebrand factor-binding protein (vWbp), and Staphylokinase (SAK), which play pivotal roles in blood coagulation, fibrinolysis, and evasion of host antibacterial peptides. Notably, these proteins contribute to the formation of fibrin networks, protecting the bacterium from immune clearance and promoting lethal bloodstream infections in murine models. Additionally, the debate surrounding the role of SAK as a critical virulence factor is addressed, emphasizing its impact on biofilm formation, invasion of internal organs, and bacterial loads in sepsis studies. Furthermore, the interaction of *S. aureus* with matrix metalloproteinases and the secretion of superantigen-like proteins (SSL1 and SSL5) are explored as additional mechanisms employed by the bacterium to impede immune responses. In addressing emerging challenges in

Abbreviations: HAIs, Healthcare-Associated Infections; MRSA, Methicillin-Resistant Staphylococcus aureus; ICUs, Intensive Care Units; GLASS, Global Antimicrobial Resistance and Use Surveillance System; NK cells, Natural Killer cells; PRRs, Pattern Recognition Receptors; TLRs, Toll-Like Receptors; NLRs, Nucleotide-Binding Oligomerisation Domain NOD-Like Receptors; RLRs, Retinoic Acid-Inducible Gene-I RIG-I-Like Receptors; AMPs, Antimicrobial Peptides; NAbs, Naturally Occurring Antibodies; KCs, Keratinocytes; PAMPs, Pathogen-Associated Molecular Patterns; IL-1, Interleukin-1; TNFα, Tumor Necrosis Factor alpha; RANKL, Receptor Activator of Nuclear Factor Kappa-B Ligand; NOD, Nucleotide-binding Oligomerization Domain; MAMPs, Microbial-Associated Molecular Patterns; MAC, Membrane Attack Complex; ScpA, Staphopain A; SspB, Staphopain B; Aur, Aureolysin; SPLs, Serine Protease–Like Proteins; SSSS, Staphylococcal Scalded Skin Syndrome; ETA, Exfoliative Toxin A; ETB, Exfoliative Toxin B; IL-8, Interleukin-8; SpyCEP, Streptococcus pyogenes homolog SpyCEP protease; Coa, Coagulase; VWbp, von Willebrand factor-binding protein; SAK, Staphylokinase; PLG, Plasminogen; T-PA, Tissue plasminogen activator; UK, Urokinase; FnBPA, Fibronectin-binding protein A; FnBPB, Fibronectin-binding protein B; IgG, Immunoglobulin G; CP, Classical pathway; LP, Lectin pathway; C4bC2, C3 proconvertase; Cna, Collagen adhesin; SCIN, Staphylococcal Complement Inhibitor; Efb, Extracellular Fibrinogen Binding Protein; SD, Serine-Aspartate; SdgA/SdgB, Staphylococcus aureus Glycosylases A/B; NETs, Neutrophil Extracellular Traps.

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innate immunity, the paper discusses the escalating antibiotic resistance in *S. aureus*, with a specific focus on methicillin-resistant strains (MRSA) and its capacity to instigate healthcare-associated infections as an effect.

1. Introduction

In recent years, an intensified focus has been placed on unravelling the interplay between microbial pathogens and the human immune system, particularly within healthcare-associated infections (HAIs) [1]. Amid the myriad pathogens that pose substantial threats to healthcare settings, *Staphylococcus aureus* has emerged as a significant protagonist, presenting formidable challenges to the innate immune response [2]. The immune system, consisting of innate and adaptive mechanisms, is the primary defence against various pathogens, including viruses, bacteria, protozoa, and fungi [3]. While innate immunity is an intrinsic defence during initial pathogenic encounters, adaptive immunity assumes responsibility for subsequent or recurrent exposures [4].

Against this backdrop, *S. aureus*, renowned for its antibiotic resistance and capacity to induce a spectrum of healthcare-associated diseases, has become a critical concern [5]. Once susceptible to beta-lactam and related antibiotic classes, the rise of methicillin-resistant *S. aureus* (MRSA) strains has precipitated a profound therapeutic conundrum [6]. Predisposing factors, such as prolonged hospitalisations, the use of indwelling medical devices, and indiscriminate antimicrobial practices, contribute to the escalating prevalence of MRSA [7]. Particularly vulnerable are patients in intensive care units (ICUs), post-surgical individuals, and those reliant on medical devices, given their compromised immune status [8].

The imperative to prevent *S. aureus* infections has gained paramount significance, with routine vaccination remaining elusive [9]. Consequently, this paper aims to comprehensively explore the challenges of *S. aureus* within healthcare-associated infections, elucidating the pathogen's evasion strategies against the innate immune response. In addition, the study endeavors to examine the implications of antibiotic resistance on therapeutic interventions and propose potential strategies for mitigating the escalating prevalence of drug-resistant *S. aureus* strains. Against this backdrop, the 2022 Global Antimicrobial Resistance and Use Surveillance System (GLASS) report revealed that MRSA constitutes 35% of median reported rates [8]. Alarming global statistics further highlight an average of 64 deaths per 100,000 individuals associated with antibiotic resistance, with Western sub-Saharan Africa recording the highest mortality at 114.8 deaths per 100,000 people. Presently, nearly 99% of *S. aureus* strains exhibit resistance to penicillin, with mecA gene-encoded strains representing the majority of MRSA strains. This surge in drug-resistant pathogens poses an imminent threat to global public health [8].

The escalating prevalence of antibiotic-resistant strains of *S. aureus*, particularly the rise of MRSA, necessitates a thorough review of the current state of knowledge. This review aims to consolidate existing literature, providing a comprehensive understanding of the mechanisms employed by *S. aureus* to subvert innate immune defences and thrive in healthcare settings. This review contributes to the broader scientific discourse on healthcare-associated infections, fostering a deeper comprehension of the challenges posed by *S. aureus* and informing future research directions in the field.

2. Methodology

A literature search of PubMed, Scopus, and Web of Science was conducted. The search focused on articles published between 2000 and December 2023 thereby making more recent articles in the 21st century the focal source due to the volume of existing work on *S. aureus*. A combination of keywords such as "*Staphylococcus aureus*," "innate immunity," "antibiotic resistance," and "healthcare-associated infections" guided the search. The inclusion criteria encompassed studies published in peer-reviewed journals. The extracted studies were categorised based on themes such as innate immune responses to *S. aureus*, antibiotic resistance mechanisms, and the dynamics of healthcare-associated infections. Although various literature have attested to the plethora of pertinent players and mechanisms involved in this cause and effect system of S. aureus to nosocomial infections, the integration of findings in this article clearly constructs a more comprehensive narrative using recent and up to date information to elucidate the challenges posed by *S. aureus* in healthcare settings, particularly focusing on innate immunity and antibiotic resistance.

2.1. Innate immune response to S. aureus

The innate immune system serves as a sophisticated defence mechanism, comprising cellular defences, humoral responses, and physical barriers that collectively establish the initial line of protection against microbes while maintaining overall body homeostasis [5]. Fig. 1. An integral component of the innate immune response is its cellular aspect, crucial for recognising and eradicating invading pathogens [6]. Key participants in this cellular defence include natural killer (NK) cells, dendritic cells, neutrophils, and macrophages [7]. Macrophages and dendritic cells, functioning as expert antigen-presenting cells, play a pivotal role in stimulating immune responses by exposing other immune cells to antigens derived from pathogens [7].

Meanwhile, NK cells specialise in identifying and eliminating virus-containing infected host cells, showcasing their proficiency in combating microbial threats [6,7]. In addition, pattern recognition receptors (PRRs) interact with microbial-associated molecular patterns (MAMPs), enabling the innate immune system to recognise pathogens [7]. Pattern recognition receptors (PRRs) that are important for the innate immune response include toll-like receptors (TLRs), nucleotide-binding oligomerisation domain (NOD)-like receptors (NLRs), and retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) [3,7].

Some interrelated elements make up the humoral arm of the innate immune response, which is essential for defending the host against pathogens, directing the adaptive immune response, and preserving general homeostasis [8]. Three pathways lead to complement activation, forming the membrane attack complex (MAC) and other immune mediators [8]. Factor XII is involved in the contact cascade, which starts clot formation and triggers several physiological reactions. B1 B lymphocytes produce naturally occurring antibodies (NAbs) to recognise various pathogens and regulate the adaptive immune response [6]. As acute phase proteins, lectraxins (serum amyloid P protein, C-reactive protein) identify and remove pathogens [5]. Although these humoral components' complex interactions are essential to host defence, improper activation can have negative consequences [9].

The skin's structural framework accommodates blood vessels, adipocytes, fibroblasts, and diverse resident immune cells, such as macrophages, dendritic cells, mast cells, T and B lymphocytes, and plasma cells [10]. The abundance of these immune cells within the skin collectively contributes to regulating *S. aureus* infection by influencing different facets of the immune response [11]. Keratinocytes (KCs), as the first line of defence, recognise pathogen-associated molecular patterns (PAMPs) through PRRs such as Toll-like receptors (TLRs), NOD1, NOD2, CD36, and MARCO [12]. Activation of these receptors produces various cytokines, chemokines, and antimicrobial effectors [13]. TLRs, particularly TLR2, are involved in multiple stages of *S. aureus* infection, inducing inflammatory responses and antimicrobial peptide release [13]. Intracellular PRRs, NOD1 and NOD2, also detect *S. aureus* peptidoglycan, triggering inflammation, antimicrobial peptide production, and

phagocytic effector functions [14]. Scavenger receptors like CD36, SRBII, and MARCO are essential for optimal skin host defence against *S. aureus* [14–16]. The distinct roles of various dendritic cell subsets in *S. aureus* skin infection have yet to be fully understood, highlighting the complexity of the immune response in the skin [17].

S. aureus has a wide range of virulence factors that help it attach to host tissues, invade those tissues, cause host cell death, and spread throughout the body. Remarkably, these virulence factors also strongly trigger the innate immune system [18]. Staphylococcal adhesins bind *S. aureus* to collagen and fibronectin, two extracellular matrix (ECM) constituents in bone. Certain adhesins even help *S. aureus* enter non-professional phagocytic cells like osteoblasts through endocytic uptake [19]. Lysing the endosome, *S. aureus* can break free and enter the cytoplasm after internalisation. Due to the expression of different PRRs by osteoblasts, osteoclasts, and their precursor cells, this intimate interaction with bone cells sets off immune responses [20]. Depending on the cell type, different outcomes can arise from PRR ligation. While PRR stimulation inhibits myeloid precursor cells from developing into osteoclasts, it improves pre-osteoclast differentiation primed with RANKL. Pro-osteoclastogenic cytokines like TNFα and RANKL are

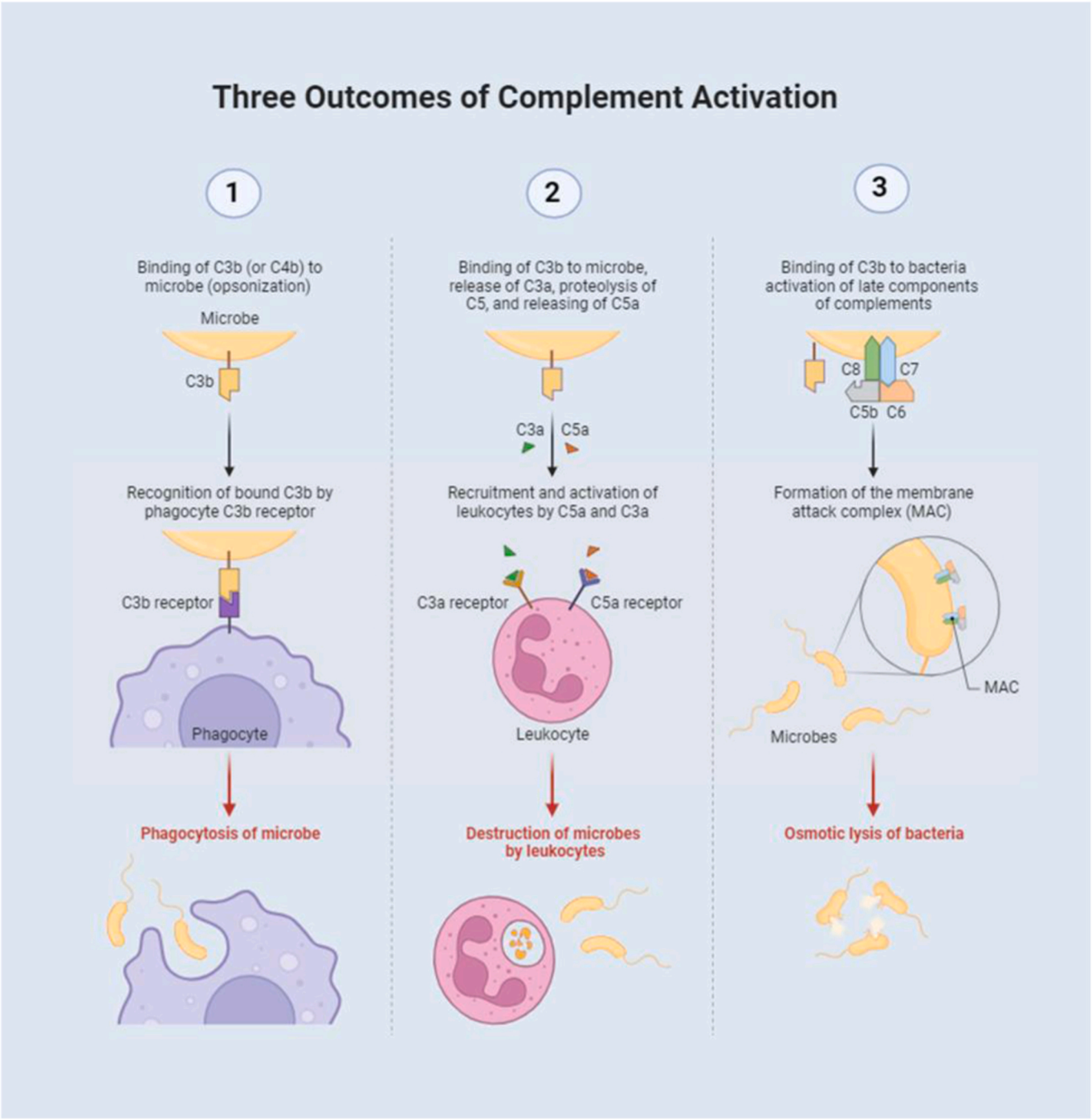

Fig. 1. Summary of the outcome of complement activation, (1) Opsonization of target cells occurs through complement cleavage products like C3b, facilitating recognition by phagocytes and subsequent phagocytosis. (2) The cleavage of C3 and C5 results in the generation of anaphylatoxins, C3a and C5a, respectively. These anaphylatoxins recruit and activate immune cells by binding to their receptors on leukocytes. (3) The late complement components, including C5, C6, C7, C8, and C9, collaborate to form the membrane attack complex (MAC), a pore structure that induces cytolysis. Image was created with Biorender.

produced when osteoblast PRR activation occurs, along with other cytokines and antimicrobial peptides (AMPs) [21]. Crosstalk may be between immune-mediated signalling and signalling cascades triggered by RANKL on myeloid cells after immune activation. Furthermore, p38 MAPK is activated by IL-1 cytokines via TRAF6 signalling, which promotes osteoclastogenesis. TLR/IL-1R ligation has a complex effect on osteoclast differentiation; however, once cells are primed with RANKL, these stimuli enhance osteoclastogenesis [22].

Bone cell PRRs that sense *S. aureus* include TLR2, which recognizes lipoteichoic acid and peptidoglycan; TLR9, which recognizes bacterial DNA endosomally; and NOD, which recognizes cytoplasmic bacteria that have escaped from the endosome [23]. In vitro, *S. aureus* activates osteoblasts' TLR2, which results in the release of AMPs and cell death [24]. Once internalized, TLR9-mediated oxidative stress induction can eradicate *S. aureus* in osteoblasts within the endosome [25]. Osteoblasts are also stimulated by *S. aureus* to express NOD2, and the combination of NOD2 and TLR2 produces RANKL. Furthermore, *S. aureus* peptidoglycan and bone particles in myeloid cells can activate the NLRP3 inflammasome. As a result, when multiple PRRs on bone cells identify *S. aureus*, a strong inflammatory response is triggered, which modifies bone remodelling. The significance of the response to general bacterial motifs is highlighted by the recognition of *S. aureus* by PRRs such as TLR2 and NOD2, which establish shared innate mechanisms between resident skin and bone cells [26,27].

2.2. Strategies employed by S. aureus against the innate immune system

S. aureus utilises an array of proteases, including cysteine proteases (staphopain A, ScpA, and staphopain B, SspB), a serine protease (V8 or SspA), serine protease–like proteins (Spls), and a metalloproteinase (aureolysin, Aur) [28]. Originally viewed as a nutrient acquisition tool, evidence now suggests their critical involvement in evading host immunity by interacting with neutrophils, plasma proteins, and antimicrobial peptides [29]. This paradigm shift highlights the multifunctional role of *S. aureus* proteases in host-pathogen interactions, immune evasion, and adaptation within the host environment [30,31].

Staphopains A (ScpA) and B (SspB) are papain-like proteases expressed by *Staphylococcus aureus,* approximately 20 kDa in size and exhibiting nearly identical three-dimensional structures despite having limited primary sequence identity. ScpA comprises two domains known as L- and R-domains [29]. While the in vivo virulence potential of staphopains remains insufficiently explored, in vitro experiments have highlighted their broad activity, encompassing connective tissue degradation, interference with clotting and kinin systems, and direct interactions with host immune cells [32,33].

In ScpA experiments, neutrophils treated with this protease exhibit a diminished response to CXCR2 chemokine activation following the specific cleavage of the N-terminal domain. Specific protease inhibitors can counteract this effect [33]. Furthermore, ScpA hampers neutrophil migration toward CXCR2 chemokines and tissue recruitment, emphasising its regulatory role in immune cell functions [34]. It is crucial to note that translating these in vitro findings to the complexities of infected tissues remains challenging due to the intricate and redundant network of cytokine functions [34].

On the other hand, exposure of phagocytes (neutrophils and monocytes) to SspB inhibits their antibacterial functions by suppressing chemotactic activity, leading to extensive clearance of SspB-treated cells by macrophages. SspB also cleaves CD31 on the surface of neutrophils, a member of the immunoglobulin superfamily involved in the repulsive signalling pathway that discourages macrophage predatory activity. Consequently, SspB's proteolytic activity compromises neutrophil functionality, explaining monocyte-derived macrophages' observed phagocytosis of SspB-treated neutrophils, facilitating staphylococcal colonisation and spreading [30].

V8 protease relates to pancreatic serine proteases, exhibiting a distinct enzymatic profile [31,32]. The enzyme's structural resemblance extends to various serine proteases, including epidermolytic toxins A and B from *S. aureus* and trypsin, with nearly identical active site conformations [33,34]. Particularly unique is the involvement of the positively charged N-terminus in determining substrate specificity [35]. V8 protease exhibits the distinctive ability to degrade all human immunoglobulin classes [34]. Its cleavage of IgG is linked to the partial loss of antigenic determinants and disruption of effector function due to Fc region degradation [35]. This suggests that V8 protease may interfere with the ability of antibodies to link cell-surface antigens to immune effector cells, potentially providing a protective mechanism for bacteria against the host's defence mechanisms [35].

Aureolysin (Aur), a zinc-dependent metalloprotease within the thermolysin family, showcases a distinctive structure with a polypeptide chain folding into a β-pleated N-terminal domain and an α-helical C-terminal domain [36]. The protease also engages with the immune system by affecting T and B lymphocytes, exhibiting inhibitory activity against immunoglobulin production [37–39]. Furthermore, Aur plays a pivotal role in staphylococcal immune evasion through the cleavage of antimicrobial peptide LL-37 [31]. Recent investigations by Burlak et al. reveal intriguing dynamics within phagocytic vacuoles. Aur, along with other staphylococcal proteases, is expressed following bacterial phagocytosis by human neutrophils [40]. This newfound insight, coupled with the observation that an isogenic aur mutant is more efficiently targeted by macrophages upon phagocytosis, suggests a potential protective mechanism where Aur shields staphylococci within phagocytes, possibly resisting antimicrobial peptide killing [41]. Delving deeper into Aur's interaction with the complement system, detailed analysis reveals its ability to cleave complement component C3 to C3b. The ensuing rapid degradation by factors H and I in serum results in poor opsonization of bacteria with C3b. This intricate process attenuates phagocytosis and subsequent killing by neutrophils [34].

Serine Protease–Like Proteins (Spls) in *Staphylococcus aureus* constitute a group of six extracellular proteases (SplA-SplF) expressed in vivo and encoded within a single operon in the *S. aureus* genome. SplA, SplB, SplC, and SplD are extensively characterised, showing structural homology to V8 protease and epidermolytic toxins [42]. For instance, SplA exhibits a chymotrypsin-like fold with two domains, each having six antiparallel β strands, forming a β barrel. The enzyme's active site includes conserved residues, characteristic of enzymatically active chymotrypsin-like proteases [42]. Spls induce IgE antibody responses in most asthmatic patients and stimulate T cells to produce TH2 cytokines, resembling typical allergen responses. This suggests that Spls could be considered triggering allergens released by *S. aureus*, presenting opportunities for asthma diagnosis and causal therapy [43].

Furthermore, Spls are crucial in causing disseminated lung damage in a rabbit pneumonia model. SplA can cleave mucin 16, a glycosylated cell surface protein from the human lung cell line CalU-3. This cleavage suggests removing mucin 16 may promote *S. aureus* invasion and spread in host tissues. Analysis of secreted and surface proteins in *S. aureus* strains revealed alterations in bacterial protein abundance, indicating a potential role of these proteases in modulating virulence factor production. The exact impact of Spls, with their proteolytic potential, on the host's immune defence mechanisms remains to be determined [44].

A homolog of a Staphylococcus epidermidis protein, annotated as an epidermin leader peptide processing serine protease (EpiP), has been identified and characterised in *Staphylococcus aureus* [45]. The *S. aureus* EpiP is released into the extracellular milieu and expressed as a zymogen that undergoes cleavage through an autocatalytic intramolecular mechanism. This protein acts as a serine protease and cleaves collagen and casein [45]. The epiP gene contains a peptidase-S8 domain in subtilisin-like serine proteases and the *Streptococcus pyogenes* homolog SpyCEP protease [45]. SpyCEP, known to inactivate IL-8 through C-terminal cleavage, hinders neutrophil recruitment at the infection site, impacting bacterial clearance. Given the crucial role of neutrophils in combating bacterial infections, EpiP might display a pathogenic activity similar to SpyCEP [46].

Exfoliative toxins A and B (ETA/ETB) directly contribute to skin breakage, causing blister formation in staphylococcal scalded skin syndrome (SSSS) and bullous impetigo. ETA and ETB, serine proteases with a similar overall structure, specifically cleave desmoglein 1, a desmosomal adhesion molecule mediating intercellular adhesion in the stratum granulosum of the skin [47]. In SSSS, *S. aureus* in distant foci produces toxins that can spread through the bloodstream and cause exfoliation in remote sites. In bullous impetigo, a localised form of SSSS, *S. aureus* is present only in the lesions [47].

ETs share a cleavage site on desmoglein 1 and a high sequence similarity with V8 protease. Therefore, it is speculated that ETs and V8 might collaborate to disrupt desmoglein 1, compromising the stability and barrier function of the skin [48]. In a variant of the above strategy, *S. aureus* cells capture activated host proteases that directly cleave essential components of host defense mechanisms. For instance, the cell wall-anchored protein clumping factor A binds to the complement regulator factor I, enhancing factor I-driven cleavage of complement component C3b [47]. Similarly, the surface protein SdrE enhances the recruitment of complement regulator factor H (FH). SdrE-bound FH retains cofactor activity for factor I-mediated cleavage of C3b, resulting in the down-regulation of complement effectors and increased protection from neutrophil killing [48].

2.3. Proteins expressed by S. aureus that modulate host protease activity

S. aureus employs a variety of proteins to modulate host protease activity, playing crucial roles in immune evasion and enhancing the pathogen's virulence. These proteins work with host systems like the complement system, the coagulation cascade, and the fibrinolysis cascade. They do this by either turning on zymogens or stopping host proteases that are important for immune defense [49,50].

Coagulation Modulators: Coa and vWbp: Von Willebrand factor-binding protein (vWbp) and coagulase (Coa) are two essential proteins that control coagulation. Coa binds prothrombin via its N-terminal D1D2 domain, inducing a conformational change that allows prothrombin to convert fibrinogen into fibrin, facilitating clot formation [51]. This creates a protective fibrin shield around the bacteria, aiding immune evasion and directly affecting the coagulation cascade [52,53]. In the same way, vWbp binds to von Willebrand factor and forms a complex with prothrombin. This complex changes fibrinogen into fibrin and helps blood clot and causes infections in the bloodstream [54].

Fibrinolysis Modulator: Staphylokinase (SAK): Staphylokinase (SAK), a bacteriophage-encoded protein, is a crucial fibrinolysis modulator. It binds to and neutralizes human antibacterial peptides, changes plasminogen into plasmin, and helps break down fibrin and important immune molecules like IgG and C3b [55–58]. SAK helps bacteria spread, stops biofilms from forming, and encourages invasion of internal organs, making it very important for staphylococcal infections [59].

Cellular Barrier Disruptor: α-Toxin: α-Toxin, also known as α-hemolysin, breaks down cell barriers by killing cells in different ways and affecting the way epithelial barriers work. It cleaves E-cadherin via the receptor ADAM10, facilitating staphylococcal invasion and contributing to the severity of acute lung injuries [60,61]. This toxin disrupts physical barriers and activates host proteases.

Neutrophil Serine Protease Inhibitor: Extracellular Adherence Protein (Eap): Extracellular adherence protein (Eap) is a neutrophil serine protease inhibitor that interferes with the activation and function of neutrophil serine proteases (NSPs) by blocking their catalytic sites [50]. This action lowers the ability of neutrophils to opsonophagocytose and kills *S. aureus,* which lets the pathogen avoid being killed by neutrophils [62,63].

Matrix Metalloprotease Inhibitors: SSL1 and SSL5: SSL proteins, particularly SSL1 and SSL5, act as matrix metalloprotease inhibitors. They inhibit matrix metalloprotease activity, affecting neutrophil chemotaxis and migration by blocking the cleavage and potentiation of IL-8 and restraining neutrophil migration [64,65]. This impairs the host's ability to clear bacterial infections.

Complement System Modulators: Cna and SCIN: Complement system modulators, such as Cna and SCIN, represent strategies employed by *S. aureus* to evade the complement system. Cna prevents the formation of the CP activation complex, while SCIN stabilizes the alternative pathway convertase in an inactive state, hindering the complement system's role in immune defense [66,67].

Other Key Proteins: Efb and Cell Wall-Anchored Proteins: Fibrinogen binding protein (Efb) disrupts the interaction between C3b and complement factor B, inhibiting active C3 convertase formation [68]. Its role in hindering platelet aggregation, impeding wound healing, and obstructing neutrophil adherence emphasizes its significance in immune evasion and infection propagation [69–71]. Cell wall-anchored proteins, including clumping factors A and B, along with the glycosylases SdgA and SdgB, enhance *S. aureus* adherence to host tissues and protect bacterial proteins from degradation by human proteases [72,73]. This mechanism supports the pathogen's colonization and persistence in the host.

S. aureus utilizes a sophisticated array of proteins to manipulate host protease activity, aiding in its survival and proliferation within the host. These proteins target critical points in the host's immune defense mechanisms, facilitating the pathogen's evasion and contributing to its virulence. Understanding these interactions offers insights into potential therapeutic targets for combating *S. aureus* infections.

3. Emerging challenges in innate immunity

3.1. Comparative analysis of S. aureus strains and their interactions with the immune system

Different *S. aureus* strains, including *methicillin-susceptible S. aureus* (MSSA), *methicillin-resistant S. aureus* (MRSA), *vancomycin-intermediate S. aureus* (VISA), and *vancomycin-resistant S. aureus* (VRSA), have intricate interactions between them and the host immune system, highlighting the emerging challenges in combating *S. aureus* infections.

MSSA strains are generally more susceptible to antibiotics compared to their resistant counterparts. However, they still possess an array of virulence factors that enable them to evade the host immune response. *S. aureus* produces several hemolytic exoproteins, such as alpha (α), beta (β), delta (δ), and gamma (γ) toxins, as well as Panton-Valentine leucocidin (PVL), which regulate tissue damage and induce inflammatory reactions [73]. These toxins contribute to the pathogenesis of MSSA infections by damaging host cells and modulating the immune response.

MRSA strains, on the other hand, have acquired resistance to methicillin and other β-lactam antibiotics, making them more challenging to treat. The emergence of community-acquired MRSA (CA-MRSA) infections has further complicated the situation, as these strains often possess additional virulence factors that enhance their pathogenicity [74]. MRSA strains have evolved various mechanisms to evade the host immune system, such as the production of protein A, which binds to the Fc region of immunoglobulins and prevents opsonization [74]. Additionally, MRSA strains often carry genes encoding toxins, such as Panton-Valentine leukocidin (PVL), which can cause severe tissue damage and necrotizing pneumonia [73].

The emergence of VISA and VRSA strains has further compounded the challenges in treating *S. aureus* infections. VISA strains have reduced susceptibility to vancomycin, which is often considered a last-resort antibiotic for treating MRSA infections. The reduced susceptibility is attributed to the thickening of the bacterial cell wall, which hinders the penetration of vancomycin [75]. VRSA strains, on the other hand, have acquired the vanA gene from enterococci, which confers high-level resistance to vancomycin [75]. The limited treatment options for VISA and VRSA infections pose a significant threat to public health.

The host immune response to *S. aureus* infections involves both innate and adaptive immunity. The innate immune system, comprising neutrophils, macrophages, and antimicrobial peptides, plays a crucial

role in the initial defense against *S. aureus* [73]. However, *S. aureus* has developed various strategies to counteract the innate immune response, such as the production of extracellular proteases that degrade antimicrobial peptides and the formation of biofilms that protect the bacteria from phagocytosis [74].

The adaptive immune response, mediated by T and B lymphocytes, is essential for the clearance of *S. aureus* infections. However, *S. aureus* has evolved mechanisms to subvert the adaptive immune response, such as the production of superantigens that cause a massive activation of T cells, leading to a cytokine storm and tissue damage [74]. Additionally, *S. aureus* can persist intracellularly within host cells, evading the humoral immune response [73].

The increasing prevalence of antibiotic-resistant *S. aureus* strains, particularly MRSA, VISA, and VRSA, has led to a growing interest in alternative therapeutic approaches, such as bacteriophage therapy and the use of nanoformulations for targeted drug delivery [73]. Bacteriophages are viruses that specifically infect and lyse bacterial cells, providing a potential alternative to antibiotics. However, the development of phage resistance and the challenges in delivering phages to the site of infection remain hurdles to overcome [73].

The comparative analysis of different *S. aureus* strains highlights the complex interactions between the bacteria and the host immune system. The emergence of antibiotic-resistant strains, such as MRSA, VISA, and VRSA, has made the treatment of *S. aureus* infections increasingly challenging. A better understanding of the virulence factors and immune evasion strategies employed by these strains is crucial for developing effective therapeutic interventions. The exploration of alternative approaches, such as bacteriophage therapy and nanoformulations, holds promise for tackling the growing threat of antibiotic-resistant S. aureus infections.

3.2. *S. aureus and MRSA evasion strategies*

S. aureus, particularly MRSA, has evolved sophisticated strategies to evade and manipulate the innate immune response, posing significant challenges for the treatment and control of infections. One key mechanism employed by *S. aureus* is the hijacking of host cell metabolism to create a favorable environment for its survival and replication. In the context of biofilm infections, *S. aureus* can induce a metabolic shift in infiltrating monocytes and macrophages toward oxidative phosphorylation, skewing them to an anti-inflammatory phenotype [76]. This metabolic reprogramming is mediated by biofilm-derived lactate, which inhibits histone deacetylase 11 (HDAC11) in myeloid-derived suppressor cells (MDSCs) and macrophages, leading to increased production of the anti-inflammatory cytokine IL-10 and promoting biofilm persistence [76]. By altering the metabolic state of innate immune cells, *S. aureus* effectively impairs their ability to mount a robust immune response and clear the infection.

In addition to manipulating host metabolism, *S. aureus* can directly modulate the function of innate immune cells. A prime example is the interaction between *S. aureus* α-toxin and macrophages. α-toxin activates the NLRP3 inflammasome in macrophages, triggering a cascade of events that ultimately leads to the redistribution of mitochondria away from phagosomes [77]. This spatial reorganization of mitochondria prevents phagosomal acidification and impairs the macrophage's ability to kill internalized bacteria [77]. Furthermore, *S. aureus* biofilms can skew the immune response towards an anti-inflammatory phenotype by inducing the recruitment and activation of MDSCs [78]. These cells suppress T-cell responses and contribute to biofilm persistence by creating an immunosuppressive microenvironment [78]. The ability of *S. aureus* to modulate innate immune cell function through various mechanisms allows the pathogen to establish chronic infections and evade clearance by the host immune system.

Neutrophils play a critical role in the host defense against *S. aureus* infections; however, MRSA strains have developed strategies to evade neutrophil-mediated killing. *S. aureus* can survive within neutrophils by resisting the oxidative burst and secreting factors that neutralize antimicrobial peptides [79]. This intracellular survival enables the bacteria to disseminate and establish infections in distant sites. Moreover, MRSA strains can induce the formation of neutrophil extracellular traps (NETs), which are composed of DNA, histones, and antimicrobial proteins [80]. While NETs are typically considered a host defense mechanism, in the context of MRSA infections, they can paradoxically contribute to disease pathogenesis by promoting tissue damage and facilitating bacterial dissemination [80]. The ability of MRSA to manipulate neutrophil function and survive within these cells is a critical factor in the persistence and severity of infections.

Biofilm formation is another major virulence factor of *S. aureus*, particularly in the context of medical device-associated infections. Biofilms are complex communities of bacteria encased in an extracellular matrix that provides protection against the host immune response and antibiotics [81]. The extracellular matrix of *S. aureus* biofilms acts as a physical barrier, impeding the penetration of immune cells and antibodies, while also sequestering antibiotics and reducing their efficacy [81]. This protective environment allows bacteria to persist and cause chronic infections that are extremely difficult to eradicate. The ability of *S. aureus* to form biofilms on various surfaces, including medical devices and damaged tissue, is a significant contributor to the morbidity and mortality associated with these infections.

The immune evasion strategies employed by *S. aureus*, particularly MRSA strains, pose significant challenges for the treatment and management of infections. The ability of MRSA to subvert the innate immune response and form biofilms contributes to the persistence and recurrence of infections, leading to increased healthcare costs and patient suffering [76,77,81]. Furthermore, the emergence of multidrug-resistant MRSA strains has severely limited treatment options, as conventional antibiotics become less effective [77]. This growing threat of antibiotic resistance highlights the urgent need for novel therapeutic strategies that target the innate immune response and bacterial metabolism.

To address these challenges, researchers are exploring immunomodulatory approaches aimed at boosting the innate immune response and overcoming the immunosuppressive effects of MRSA. For example, the use of Toll-like receptor (TLR) agonists or cytokine therapies could potentially enhance the host's ability to clear infections by stimulating the production of pro-inflammatory mediators and activating innate immune cells [77,78]. Additionally, targeting bacterial metabolic pathways that are essential for virulence and survival, such as the agr quorum-sensing system or the stringent response, could provide new avenues for the development of anti-infective therapies [77,81]. By disrupting these key metabolic pathways, it may be possible to render MRSA more susceptible to the host immune response and antibiotics.

From a public health perspective, the increasing prevalence of CA-MRSA infections is a growing concern. CA-MRSA strains are highly virulent and can cause severe infections in otherwise healthy individuals, leading to significant morbidity and mortality [77]. To combat the spread of MRSA in both healthcare and community settings, a multi-faceted approach is necessary. This includes implementing strict infection control practices, such as hand hygiene and environmental cleaning, and developing effective antibiotic stewardship programs to reduce the selective pressure for the emergence of resistant strains [77]. Public education on proper hygiene and wound care is also crucial, particularly in high-risk populations such as athletes and individuals living in close quarters.

The ability of *S. aureus*, especially MRSA strains, to evade and manipulate the innate immune response through various mechanisms presents significant challenges for treating and controlling infections. The complex interplay between *S. aureus* and the host immune system involves the hijacking of host metabolism, modulation of innate immune cell function, evasion of neutrophil killing, and the formation of protective biofilms. These factors contribute to the persistence and recurrence of infections, leading to increased morbidity, mortality, and healthcare costs. To effectively combat this formidable pathogen, a

deeper understanding of the underlying mechanisms of immune evasion is essential. This knowledge will inform the development of novel therapeutic strategies, such as immunomodulatory therapies and targeted inhibition of bacterial metabolic pathways, as well as guide public health interventions to prevent the spread of MRSA in healthcare and community settings. Only through a comprehensive and collaborative approach involving basic research, clinical medicine, and public health can we overcome the challenges posed by *S. aureus* and MRSA infections in the era of increasing antibiotic resistance.

3.3. Challenges posed by antibiotic-resistant MRSA on healthcare and community settings

The problems caused by *S. aureus* becoming more resistant to antibiotics, especially the appearance of dangerous and drug-resistant strains like MRSA, are significant for people's health. These implications extend to both healthcare and community settings, where MRSA infections have become increasingly prevalent, leading to substantial epidemiological, infection-control, and therapeutic management challenges [76]. Also,the fact that MRSA strains cause skin and skin structure infections that come back often, even when specific antibodies and T cells are present, shows that traditional adaptive immunity is ineffective at protecting against infections. This is why targeted immunotherapeutic strategies are needed to deal with the problem of MRSA [77]. More research needs to be done on how *S. aureus* and innate immunity interact, focusing on immunometabolism and finding possible therapeutic targets [81]. Learning how skin-specific unsaturated fatty acids boost the natural immune response against *S. aureus* shows that there may be new ways to improve the host's defense mechanisms [77]. In general, to lessen the effects of these problems on people's health, we need to be proactive, use targeted immunotherapeutic strategies, keep studying how *S. aureus* and innate immunity interact, and look for new ways to boost the host's defenses. These insights support the development of targeted immunotherapeutic strategies to address the challenge of MRSA infection [77]. MRSA has created significant epidemiological, infection-control, and therapeutic management challenges during the past three decades [76]. Additionally, the persistence, antibiotic tolerance, and immune avoidance of bacterial infections associated with implanted medical devices exacerbate the healthcare crisis [79].

4. Strategies to enhance innate immunity

Over the years, MRSA has become a serious cause of hospital-associated infections, with significantly high morbidity and mortality rates [82]. Table 1. The central part of antimicrobial host response and defense is macrophage function [83]. Macrophages release proinflammatory cytokines which activate diverse immune cells which help to counter *S. aureus.* However, the excessive inflammatory response by macrophages evoked by *S. aureus,* oftentimes results in tissue injury in the host body [84]. With the evolution of challenges in innate immunity against *S. aureus,* especially in the aspect of healthcare-associated infections (HAI), requires a bold approach and innovation of strategies to help toughen the body's first line of defense against bacterial infection.

4.1. Implications for healthcare practices and future directions

The ability of *Staphylococcus aureus* to evade immunity significantly contributes to the persistence of infections, elevating the risk of colonization and transmission within healthcare settings [14]. Particularly concerning is its propensity for hematogenous seeding, notably in prosthetic valves, which contributes to healthcare-associated bacteremia and complicates treatment outcomes [111]. While many *Staphylococcus aureus* infections are minor, a subset represents a significant risk to patients, manifesting as severe cases such as bloodstream infections, pneumonia, and bone or joint infections [112]. These severe infections pose a direct threat to patient health, necessitating prompt and effective management strategies.

Table 1
Strategies to Enhance Innate Immunity.

Strategy	Mechanism	Potential Effectiveness
1. Immunomodulatory agents	Antimicrobial peptides (AMP) are a vast collection of peptides participating in diverse aspects of innate immunity [85–89]. They exhibit a broad-spectrum anti-microbial activity against microorganisms, including Gram-positives like *S. aureus* and gram-negative bacteria [84].	Ability to combat antibiotic-resistant infections such as MRSA. However, some bacteria have developed resistance mechanisms, such as secreting proteases, which can reduce the effectiveness [90]
1. Microbiome modulation	Prebiotics and probiotics shape the human microbiome, influencing innate immunity. Lactobacilli co-colonization dampens immune reactivity [91]. Probiotics such as lactobacilli mediate their immune-modulatory effects via inducing regulatory cytokines like IL-10 [92, 93], inducing Treg-cells [94–96], APC modulation [97–99], epithelial functioning and development [99], and pro-inflammatory cytokine inhibition.	Modulating the microbiome with probiotics and prebiotics hinders *S. aureus* colonization and enhances innate immune response. Probiotics inhibit MRSA growth, providing adjunct therapy to antibiotics
1. Nanoparticles for improving antibiotic delivery.	Nanoparticles enhance antibiotic stability, delay circulation time, increase specificity at target sites, and accumulate in infected tissues, minimizing adverse effects [100–102]. They overcome bacterial resistance by evading drug degradation enzymes such as beta-lactamase [103, 104], inhibiting efflux pump [105,106], and penetrating thick cell walls [106,107].	Effective drug delivery into cells or tissues through a sustained release action makes its therapeutic impact more successful. By evading degradation enzymes and inhibiting efflux pumps, nanoparticles improve drug delivery and penetration, possibly overcoming the limitations of standard antibiotics.
1. Non-pharmacological interventions	Hand hygiene, maintaining a safe, clean, hygienic hospital environment, antibiotic stewardship, public health surveillance and following safety guidelines [108,109].	These interventions offer a holistic approach to prevent and control healthcare-associated infections. Through adherence and observation, transmission rates can be reduced, leading to improved patient outcomes.
1. Targeted drug approaches	Targeted drug approaches specifically neutralize or inhibit virulence factors and disrupt biofilm formation of *S.aureus* [110].	By neutralizing these factors, targeted drugs can reduce the pathogenicity of *S. aureus*, leading to improved treatment outcomes and decreased severity of infections

Impaired innate immunity against *Staphylococcus aureus* can lead to broader-spectrum antibiotic usage, contributing to the emergence of multidrug-resistant (MDR) strains [14]. The implementation of

antibiotic stewardship programs assumes paramount importance in advocating prudent antibiotic usage to curb resistance development [113]. This entails adopting a three-pronged strategy, encompassing judicious antibiotic selection, guided by strain specificity, and ensuring the completion of treatment courses [114,115].

The potential for delayed diagnosis due to obscured symptoms and the looming risk of treatment failure underscore the criticality of rapid and accurate diagnostic methodologies [116,117]. Cutting-edge technologies such as the FDA-approved BinaxNow test offer promising avenues for swiftly identifying *Staphylococcus aureus*, facilitating targeted treatment interventions and curtailing unnecessary broad-spectrum antibiotic deployment [118].

Healthcare-associated infections (HAIs) and multidrug-resistant *S aureus* infections impose a strain on healthcare resources, resulting in treatment failures, complications, prolonged hospitalization periods, and increased mortality rates [119,120]. Addressing this multifaceted problem requires comprehensive strategies encompassing prevention, diagnosis, and treatment.

The presence of multiple virulence factors in *Staphylococcus aureus*, including staphylococcal protein A (SpA), poses challenges to the development of an effective vaccine [121]. To control the spread of *Staphylococcus aureus*, important measures such as regular handwashing, proper use of personal protective equipment (PPE), and thorough environmental cleaning are essential [122,123].

Researchers are exploring new possibilities for antibiotics to combat *Staphylococcus aureus* by focusing on vulnerabilities like biofilm defenses and toxin weapons [113,124]. The stimulation of the innate immune system via immunomodulatory therapies emerges as a promising avenue in fortifying natural defenses against *Staphylococcus aureus* infections [125]. Despite the formidable challenges in devising a universal vaccine, current research endeavors are directed towards the identification of novel formulations capable of eliciting robust immune responses tailored to combat specific strains [126,127]. Furthermore, the exploration of monoclonal antibodies targeting virulence factors offers supplementary pathways in mitigating bacterial burdens and curtailing infection rates [128,129].

5. Conclusion

S aureus is a major pathogen involved in a wide range of human infections including inflammatory diseases (skin and soft tissue infections, pneumonia, osteomyelitis, urinary tract infections, medical implant-associated infections), Toxin-mediated diseases (toxic shock syndrome, scalded skin syndrome, rapid-onset food poisoning), and the dreaded MRSA infection. It has significantly elevated the occurrence of community and nosocomial infections due to its superfluous ability to subvert the host's innate immune system. These challenges also have implications for healthcare practice, which mandates fully-formed strategies around preventative infection control, judicious antibiotic use, and early diagnosis. The ability of the bacteria to be spread hematogenously and for treatment to be overly long and damaging reaffirms that close surveillance is necessary to implement focus interventions. In addition, this burden on the healthcare system demonstrates that preventative techniques must remain at the forefront, followed by new technologies to treat and prevent. Enhancements in antibiotic therapy and immunotherapeutic modalities offer promising avenues against *S. aureus* infections. These measures emphasize the importance of continued research and innovation in addressing these pressing healthcare challenges.

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Author contributions

MIA conceptualised the study; All authors were involved in the literature review and extracted the data from the reviewed studies; All authors wrote the final and first drafts. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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References

[1] S. Uthaisangsook, N.K. Day, S.L. Bahna, R.A. Good, S. Haraguchi, Innate immunity and its role against infections. Annals of Allergy, Asthma Immunol. 88 (3) (2002 Mar 1) 253–265. Available from: https://www.sciencedirect.com/science/article/abs/pii/S1081120610620054.

[2] G. Pietrocola, G. Nobile, S. Rindi, P. Speziale, Staphylococcus aureus manipulates innate immunity through own and host-expressed proteases, Front. Cell. Infect. Microbiol. (2017 May 5) [cited 2019 Aug 11];7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5418230/.

[3] World Health Organization. Antimicrobial resistance [Internet]. World Health Organization. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.

[4] S. Rao, L. Linke, R. Magnuson, L. Jauch, D.R. Hyatt, Antimicrobial resistance and genetic diversity of Staphylococcus aureus collected from livestock, poultry and humans, One Health 15 (2022 Dec 1) 100407. Available from: https://www.sciencedirect.com/science/article/pii/S2352771422000398.

[5] J.S. Marshall, R. Warrington, W. Watson, H.L. Kim, An introduction to immunology and immunopathology, Allergy Asthma Clin. Immunol. 14 (Suppl 2) (2018) 49.

[6] R. Medzhitov, C. Janeway, Innate Immunity, N. Engl. J. Med. 343 (5) (2000) 338–344.

[7] D. Li, M. Wu, Pattern recognition receptors in health and diseases, Signal Transduct. Target Ther. 6 (1) (2021) 291.

[8] M. Vestergaard, D. Frees, H. Ingmer, Antibiotic Resistance and the MRSA Problem, Microbiol. Spectr. 7 (2) (2019 Mar 22), https://doi.org/10.1128/microbiolspec.gpp3-0057-2018.

[9] S.N. Shishido, S. Varahan, K. Yuan, X. Li, S.D. Fleming, Humoral innate immune response and disease, Clin. Immunol. 144 (2) (2012) 142–158.

[10] M. Pasparakis, I. Haase, F.O. Nestle, Mechanisms regulating skin immunity and inflammation, Nat. Rev. Immunol. 14 (5) (2014) 289–301.

[11] A. Matejuk, Skin Immunity, Arch. Immunol. Ther. Exp. (Warsz.) 66 (1) (2018) 45–54.

[12] F. Ibrahim, T. Khan, G.G. Pujalte, Bacterial Skin Infections, Prim. Care 42 (4) (2015) 485–499.

[13] K. Bitschar, C. Wolz, B. Krismer, A. Peschel, B. Schittek, Keratinocytes as sensors and central players in the immune defense against Staphylococcus aureus in the skin, J. Dermatol. Sci. 87 (3) (2017) 215–220.

[14] M.J. Castleman, M. Febbraio, P.R. Hall, CD36 is essential for regulation of the host innate response to staphylococcus aureus α-toxin-mediated dermonecrosis, J. Immunol. 195 (5) (2015) 2294–2302.

[15] H. Schäffler, D.D. Demircioglu, D. Kühner, S. Menz, A. Bender, I.B. Autenrieth, et al., NOD2 stimulation by Staphylococcus aureus-derived peptidoglycan is boosted by Toll-like receptor 2 costimulation with lipoproteins in dendritic cells, Infect. Immun. 82 (11) (2014) 4681–4688.

[16] S.L. Brandt, N.E. Putnam, J.E. Cassat, C.H. Serezani, Innate Immunity to Staphylococcus aureus: evolving Paradigms in Soft Tissue and Invasive Infections, J. Immunol. 200 (12) (2018) 3871–3880.

[17] S.D. Kobayashi, N. Malachowa, F.R. DeLeo, Pathogenesis of Staphylococcus aureus abscesses, Am. J. Pathol. 185 (6) (2015) 1518–1527.

[18] L. Thomer, O. Schneewind, D. Missiakas, Pathogenesis of staphylococcus aureus bloodstream infections, Annu. Rev. Pathol. 11 (2016) 343–364.

[19] J. Josse, F. Velard, S.C. Gangloff, Staphylococcus aureus vs. osteoblast: relationship and consequences in osteomyelitis, Front. Cell Infect. Microbiol 5 (2015) 85.

[20] P.D. Kim, X. Xia-Juan, K.E. Crump, T. Abe, G. Hajishengallis, S.E. Sahingur, Toll-like receptor 9-mediated inflammation triggers alveolar bone loss in experimental murine periodontitis, Infect. Immun. 83 (7) (2015) 2992–3002.

[21] Z. Bar-Shavit, Taking a toll on the bones: regulation of bone metabolism by innate immune regulators, Autoimmunity 41 (3) (2008) 195–203.

[22] Y. Kadono, F. Okada, C. Perchonock, H.D. Jang, S.Y. Lee, N. Kim, et al., Strength of TRAF6 signalling determines osteoclastogenesis, EMBO Rep. 6 (2) (2005) 171–176.

[23] P. Zhang, J. Liu, Q. Xu, G. Harber, X. Feng, S.M. Michalek, et al., TLR2-dependent modulation of osteoclastogenesis by Porphyromonas gingivalis through differential induction of NFATc1 and NF-kappaB, J. Biol. Chem. 286 (27) (2011) 24159–24169.

[24] Q. Chen, T. Hou, F. Luo, X. Wu, Z. Xie, J. Xu, Involvement of toll-like receptor 2 and pro-apoptotic signaling pathways in bone remodeling in osteomyelitis, Cell Physiol. Biochem 34 (6) (2014) 1890–1900.

[25] W. Mohamed, E. Domann, T. Chakraborty, G. Mannala, K.S. Lips, C. Heiss, et al., TLR9 mediates S. aureus killing inside osteoblasts via induction of oxidative stress, BMC Microbiol 16 (1) (2016) 230.

[26] A. Kassem, P. Henning, P. Lundberg, P.P. Souza, C. Lindholm, U.H. Lerner, Porphyromonas gingivalis Stimulates Bone Resorption by Enhancing RANKL (Receptor Activator of NF-κB Ligand) through Activation of Toll-like Receptor 2 in Osteoblasts, J. Biol. Chem. 290 (33) (2015) 20147–20158.

[27] Y. Alippe, C. Wang, B. Ricci, J. Xiao, C. Qu, W. Zou, et al., Bone matrix components activate the NLRP3 inflammasome and promote osteoclast differentiation, Sci. Rep. 7 (1) (2017) 6630.

[28] L. Shaw, E. Golonka, J. Potempa, S.J. Foster, The role and regulation of the extracellular proteases of Staphylococcus aureus, Microbiology 150 (1) (2004) 217–228.

[29] I. Massimi, E. Park, K. Rice, W. Muller-Esterl, D. Sauder, M.J. McGavin, Identification of a Novel Maturation Mechanism and Restricted Substrate Specificity for the SspB Cysteine Protease ofStaphylococcus aureus, J. Biol. Chem. 277 (44) (2002) 41770–41777.

[30] Smagur J., Guzik K., Bzowska M., Kuzak M., Zarebski M., Kantyka T., et al. Staphylococcal cysteine protease staphopain B (SspB) induces rapid engulfment of human neutrophils and monocytes by macrophages. 2009.

[31] M. Sieprawska-Lupa, P. Mydel, K. Krawczyk, K. Wójcik, M. Puklo, B. Lupa, et al., Degradation of human antimicrobial peptide LL-37 by Staphylococcus aureus-derived proteinases, Antimicrob. Agents Chemother. 48 (12) (2004) 4673–4679.

[32] R. Filipek, M. Rzychon, A. Oleksy, M. Gruca, A. Dubin, J. Potempa, et al., The staphostatin-staphopain complex: a forward binding inhibitor in complex with its target cysteine protease, J. Biol. Chem. 278 (42) (2003) 40959–40966.

[33] Kantyka T., Shaw L.N., Potempa J. Papain-like proteases of Staphylococcus aureus. Cysteine Proteases of Pathogenic Organisms. 2011:1-14.

[34] A.J. Laarman, G. Mijnheer, J.M. Mootz, W.J. Van Rooijen, M. Ruyken, C. L. Malone, et al., Staphylococcus aureus Staphopain A inhibits CXCR2-dependent neutrophil activation and chemotaxis, EMBO J. 31 (17) (2012) 3607–3619.

[35] L. Prasad, Y. Leduc, K. Hayakawa, L.T. Delbaere, The structure of a universally employed enzyme: V8 protease from Staphylococcus aureus, Acta Crystallogr. Sect. D: Biol. Crystallogr. 60 (2) (2004) 256–259.

[36] A. Banbula, J. Potempa, J. Travis, C. Fernandez-Catalén, K. Mann, R. Huber, et al., Amino-acid sequence and three-dimensional structure of the Staphylococcus aureus metalloproteinase at 1.72 Å resolution, Structure 6 (9) (1998) 1185–1193.

[37] J. Potempa, W. Watorek, J. Travis, The inactivation of human plasma alpha 1-proteinase inhibitor by proteinases from Staphylococcus aureus, J. Biol. Chem. 261 (30) (1986) 14330–14334.

[38] Z. Wegrzynowicz, P. Heczko, G. Drapeau, J. Jeljaszewicz, G. Pulverer, Prothrombin activation by a metalloprotease from Staphylococcus aureus, J. Clin. Microbiol. 12 (2) (1980) 138–139.

[39] L. Prokešová, Z. Porwit-Bóbr, K. Baran, J. Potempa, M. Pospíšil, C. John, Effect of metalloproteinase from Staphylococcus aureus on in vitro stimulation of human lymphocytes, Immunol. Lett. 27 (3) (1991) 225–230.

[40] C. Burlak, C.H. Hammer, M.A. Robinson, A.R. Whitney, M.J. McGavin, B. N. Kreiswirth, et al., Global analysis of community-associated methicillin-resistant Staphylococcus aureus exoproteins reveals molecules produced in vitro and during infection, Cell. Microbiol. 9 (5) (2007) 1172–1190.

[41] M. Kubica, K. Guzik, J. Koziel, M. Zarebski, W. Richter, B. Gajkowska, et al., A potential new pathway for Staphylococcus aureus dissemination: the silent survival of S. aureus phagocytosed by human monocyte-derived macrophages, PLoS One 3 (1) (2008) e1409.

[42] J. Stec-Niemczyk, K. Pustelny, M. Kisielewska, M. Bista, K.T. Boulware, H. R. Stennicke, et al., Structural and functional characterization of SplA, an exclusively specific protease of Staphylococcus aureus, Biochem. J. 419 (3) (2009) 555–564.

[43] S. Stentzel, A. Teufelberger, M. Nordengrün, J. Kolata, F. Schmidt, K. Van Crombruggen, et al., Staphylococcal serine protease–like proteins are pacemakers of allergic airway reactions to Staphylococcus aureus, J. Allergy Clin. Immunol. 139 (2) (2017) 492–500, e8.

[44] A.E. Paharik, W. Salgado-Pabon, D.K. Meyerholz, M.J. White, P.M. Schlievert, A. R. Horswill, The Spl serine proteases modulate staphylococcus aureus protein production and virulence in a rabbit model of pneumonia, mSphere 1 (5) (2016).

[45] M.L. Kuhn, P. Prachi, G. Minasov, L. Shuvalova, J. Ruan, I. Dubrovska, et al., Structure and protective efficacy of the Staphylococcus aureus autocleaving protease EpiP, FASEB J. 28 (4) (2014) 1780.

[46] A.S. Zinkernagel, A.M. Timmer, M.A. Pence, J.B. Locke, J.T. Buchanan, C. E. Turner, et al., The IL-8 protease SpyCEP/ScpC of group A Streptococcus promotes resistance to neutrophil killing, Cell Host Microbe 4 (2) (2008) 170–178.

[47] M. Amagai, K. Nishifuji, T. Yamaguchi, Y. Hanakawa, M. Sugai, J.R. Stanley, Staphylococcal exfoliative toxin B specifically cleaves desmoglein 1, J. Invest. Dermatol. 118 (5) (2002) 845–850.

[48] Y. Katayama, T. Baba, M. Sekine, M. Fukuda, K. Hiramatsu, Beta-hemolysin promotes skin colonization by Staphylococcus aureus, J. Bacteriol. 195 (6) (2013) 1194–1203.

[49] P.S. Hair, M.D. Ward, O.J. Semmes, T.J. Foster, K.M. Cunnion, Staphylococcus aureus clumping factor A binds to complement regulator factor I and increases factor I cleavage of C3b, J. Infect. Dis. 198 (1) (2008) 125–133.

[50] J.A. Sharp, C.G. Echague, P.S. Hair, M.D. Ward, J.O. Nyalwidhe, J.A. Geoghegan, et al., Staphylococcus aureus surface protein SdrE binds complement regulator factor H as an immune evasion tactic, PLoS One 7 (5) (2012) e38407.

[51] V. Nizet, Understanding how leading bacterial pathogens subvert innate immunity to reveal novel therapeutic targets, J. Allergy Clin. Immunol. 120 (1) (2007) 13–22.

[52] R. Friedrich, P. Panizzi, P. Fuentes-Prior, K. Richter, I. Verhamme, P.J. Anderson, et al., Staphylocoagulase is a prototype for the mechanism of cofactor-induced zymogen activation, Nature 425 (6957) (2003) 535–539.

[53] J. Bjerketorp, M. Nilsson, As Ljungh, J.-I. Flock, K. Jacobsson, L. Frykberg, A novel von Willebrand factor binding protein expressed by Staphylococcus aureus, Microbiology 148 (7) (2002) 2037–2044.

[54] D.A. Stapels, K.X. Ramyar, M. Bischoff, M. von Köckritz-Blickwede, F.J. Milder, M. Ruyken, et al., Staphylococcus aureus secretes a unique class of neutrophil serine protease inhibitors, Proc. Natl. Acad. Sci. 111 (36) (2014) 13187–13192.

[55] J.N. Walker, H.A. Crosby, A.R. Spaulding, W. Salgado-Pabón, C.L. Malone, C. B. Rosenthal, et al., The Staphylococcus aureus ArlRS two-component system is a novel regulator of agglutination and pathogenesis, PLoS Pathog. 9 (12) (2013) e1003819.

[56] D. Rittirsch, M.A. Flierl, P.A. Ward, Harmful molecular mechanisms in sepsis, Nat. Rev. Immunol. 8 (10) (2008) 776–787.

[57] M.I. Bokarewa, T. Jin, A. Tarkowski, Staphylococcus aureus: staphylokinase, Int. J. Biochem. Cell Biol. 38 (4) (2006) 504–509.

[58] G. Pietrocola, G. Nobile, V. Gianotti, M. Zapotoczna, T.J. Foster, J.A. Geoghegan, et al., Molecular interactions of human plasminogen with fibronectin-binding protein B (FnBPB), a fibrinogen/fibronectin-binding protein from Staphylococcus aureus, J. Biol. Chem. 291 (35) (2016) 18148–18162.

[59] S. Rooijakkers, W. Van Wamel, M. Ruyken, K. Van Kessel, J. Van Strijp, Anti-opsonic properties of staphylokinase, Microbes Infect. 7 (3) (2005) 476–484.

[60] A. Santala, J. Saarinen, P. Kovanen, P. Kuusela, Activation of interstitial collagenase, MMP-1, by Staphylococcus aureus cells having surface-bound plasmin: a novel role of plasminogen receptors of bacteria, FEBS Lett. 461 (3) (1999) 153–156.

[61] T. Jin, M. Bokarewa, L. McIntyre, A. Tarkowski, G.R. Corey, L.B. Reller, et al., Fatal outcome of bacteraemic patients caused by infection with staphylokinase-deficient Staphylococcus aureus strains, J. Med. Microbiol. 52 (10) (2003) 919–923.

[62] B.V. Geisbrecht, B.Y. Hamaoka, B. Perman, A. Zemla, D.J. Leahy, The crystal structures of EAP domains from Staphylococcus aureus reveal an unexpected homology to bacterial superantigens, J. Biol. Chem. 280 (17) (2005) 17243–17250.

[63] J.R. Fitzgerald, S.D. Reid, E. Ruotsalainen, T.J. Tripp, M. Liu, R. Cole, et al., Genome diversification in Staphylococcus aureus: molecular evolution of a highly variable chromosomal region encoding the staphylococcal exotoxin-like family of proteins, Infect. Immun. 71 (5) (2003) 2827–2838.

[64] R.J. Williams, J.M. Ward, B. Henderson, S. Poole, B.P. O'Hara, M. Wilson, et al., Identification of a novel gene cluster encoding staphylococcal exotoxin-like proteins: characterization of the prototypic gene and its protein product, SET1, Infect. Immun. 68 (8) (2000) 4407–4415.

[65] J. Bestebroer, M.J. Poppelier, L.H. Ulfman, P.J. Lenting, C.V. Denis, K.P. van Kessel, et al., Staphylococcal superantigen-like 5 binds PSGL-1 and inhibits P-selectin–mediated neutrophil rolling, Blood 109 (7) (2007) 2936–2943.

[66] K.J. Koymans, A. Bisschop, M.M. Vughs, K.P. Van Kessel, C.J. De Haas, J.A. Van Strijp, Staphylococcal superantigen-like protein 1 and 5 (SSL1 & SSL5) limit neutrophil chemotaxis and migration through MMP-inhibition, Int. J. Mol. Sci. 17 (7) (2016) 1072.

[67] Y.-P. Ko, X. Liang, C.W. Smith, J.L. Degen, M. Höök, Binding of Efb from Staphylococcus aureus to fibrinogen blocks neutrophil adherence, J. Biol. Chem. 286 (11) (2011) 9865–9874.

[68] M. Kang, Y.-P. Ko, X. Liang, C.L. Ross, Q. Liu, B.E. Murray, et al., Collagen-binding microbial surface components recognizing adhesive matrix molecule

(MSCRAMM) of Gram-positive bacteria inhibit complement activation via the classical pathway, J. Biol. Chem. 288 (28) (2013) 20520–20531.
[69] S.H. Rooijakkers, M. Ruyken, A. Roos, M.R. Daha, J.S. Presanis, R.B. Sim, et al., Immune evasion by a staphylococcal complement inhibitor that acts on C3 convertases, Nat. Immunol. 6 (9) (2005) 920–927.
[70] O. Shannon, A. Uekötter, J.-I. Flock, Extracellular fibrinogen binding protein, Efb, from Staphylococcus aureus as an antiplatelet agent in vivo, Thromb. Haemost. 93 (05) (2005) 927–931.
[71] M. Hammel, G. Sfyroera, D. Ricklin, P. Magotti, J.D. Lambris, B.V. Geisbrecht, A structural basis for complement inhibition by Staphylococcus aureus, Nat. Immunol. 8 (4) (2007) 430–437.
[72] H. Chen, D. Ricklin, M. Hammel, B.L. Garcia, W.J. McWhorter, G. Sfyroera, et al., Allosteric inhibition of complement function by a staphylococcal immune evasion protein, Proc. Natl. Acad. Sci. USA 107 (41) (2010) 17621–17626.
[73] R. Patil, D. Dehari, A. Chaudhuri, D.N. Kumar, D. Kumar, S. Singh, G. Nath, A. K. Agrawal, Recent advancements in nanotechnology-based bacteriophage delivery strategies against bacterial ocular infections, Microbiol. Res. 273 (2023) 127413, https://doi.org/10.1016/j.micres.2023.127413.
[74] N. Noori Goodarzi, N. Bolourchi, S. Fereshteh, A. Soltani Shirazi, M.R. Pourmand, F. Badmasti, Investigation of novel putative immunogenic targets against Staphylococcus aureus using a reverse vaccinology strategy, Infect., Genet. Evol. 96 (2021) 105149, https://doi.org/10.1016/j.meegid.2021.105149.
[75] W.A. McGuinness, N. Malachowa, F.R. DeLeo, Vancomycin Resistance in Staphylococcus aureus, Yale J. Biol. Med 90 (2) (2017) 269–281. Published 2017 Jun 23.
[76] M. Nguyen, D. Hanzelmann, T. Härtner, A. Peschel, F. Götz, Skin-specific unsaturated fatty acids boost the Staphylococcus aureus innate immune response, Infect. Immun. 84 (1) (2016) 205–215, https://doi.org/10.1128/iai.00822-15.
[77] C. Horn, T. Kielian, Crosstalk between Staphylococcus aureus and innate immunity: focus on immunometabolism, Front. Immunol. 11 (2021), https://doi.org/10.3389/fimmu.2020.621750.
[78] L. Chan, S. Chaili, S. Filler, L. Miller, N. Solis, H. Wang, et al., Innate immune memory contributes to host defense against recurrent skin and skin structure infections caused by methicillin-resistant Staphylococcus aureus, Infect. Immun. 85 (2) (2017), https://doi.org/10.1128/iai.00876-16.
[79] M. Abdelmaksoud, M. El-Shokry, G. Ismail, S. Hafez, A. El-Kholy, E. Attia, et al., Methicillin-resistant Staphylococcus aureus recovered from healthcare- and community-associated infections in Egypt, Int. J. Bacteriol. 2016 (2016) 1–5, https://doi.org/10.1155/2016/5751785.
[80] V.O. Baede, M.M. Voet, T.J.K. van der Reijden, et al., The survival of epidemic and sporadic MRSA on human skin mimics is determined by both host and bacterial factors, Published 2022 Nov 16. Epidemiol. Infect. 150 (2022) e203 https://doi.org/10.1017/S0950268822001765.
[81] W.L. Hazenbos, K.K. Kajihara, R. Vandlen, J.H. Morisaki, S.M. Lehar, M. J. Kwakkenbos, et al., Novel staphylococcal glycosyltransferases SdgA and SdgB mediate immunogenicity and protection of virulence-associated cell wall proteins, PLoS Pathog. 9 (10) (2013) e1003653.
[82] S. Park, J. Rich, F. Hanses, J. Lee, Defects in innate immunity predispose c57bl/6j-leprdb/leprdbmice to infection by Staphylococcus aureus, Infect. Immun. 77 (3) (2009) 1008–1014, https://doi.org/10.1128/iai.00976-08.
[83] C. Gries, Z. Rivas, D. Lo, Intra-vital multiphoton examination of implant-associated Staphylococcus aureus biofilm infection, Front. Cell. Infect. Microbiol. 10 (2020), https://doi.org/10.3389/fcimb.2020.574092.
[84] M.J. Sheppard, Control of methicillin-resistant Staphylococcus aureus, J. Hosp. Infect. 25 (2011) 155–179 ([Google Scholar] [CrossRef]).
[85] Y. Zhang, X.X. Li, Y. Ma, J. Xu, L.N. Zhao, X.F. Qian, X.F. Zhang, J.F. Shi, Q. Z. Han, CP and CP-PGN protect mice against MRSA infection by inducing M1 macrophages, Sci. Rep. 7 (2017) 16877 ([Google Scholar] [CrossRef] [PubMed] [Green Version]).
[86] X. Jiang, Y. Wang, Y. Qin, W. He, A. Benlahrech, Q. Zhang, X. Jiang, Z. Lu, G. Ji, Y. Zheng, Micheliolide provides protection of mice against Staphylococcus aureus and MRSA infection by down-regulating inflammatory response, Sci. Rep. 7 (2017) 41964.
[87] K.A. Brogden, Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? Nat. Rev. Microbiol 3 (2005) 238–250 ([PubMed] [Google Scholar]).
[88] G. Diamond, D. Laube, M.E. Klein-Patel, in: R.E.W. Hancock, D.A. Devine (Eds.), In: Mammalian Host Defence Peptides, Vol. 6, Cambridge University Press; UK: Cambridge, 2004, pp. 111–138.
[89] R.E.W. Hancock, G. Diamond, The role of cationic antimicrobial peptides in innate host defences, Trends Microbiol 8 (2000) 402–410.
[90] J. Turner, Y. Cho, N.N. Dinh, A.J. Waring, R.I. Lehrer, Activities of LL-37, a cathelin-associated antimicrobial peptide of human neutrophils, Antimicrob. Agents Chemother. 42 (1998) 2206–2214.
[91] A. Giacometti, O. Cirioni, M.S. Del Prete, A.M. Paggi, M.M. D'Errico, G. Scalise, Combination studies between polycationic peptides and clinically used antibiotics against Gram-positive and Gram-negative bacteria, Peptides 21 (2000) 1155–1160.
[92] M.A. Johansson, S. Saghafian-Hedengren, Y. Haileselassie, S. Roos, M. Troye-Blomberg, C. Nilsson, et al., Early-life gut bacteria associate with IL-4-, IL-10- and IFN-γ production at two years of age, PLoS One 7 (2012) e49315, https://doi.org/10.1371/journal.pone.0049315.
[93] Y. Haileselassie, M.A. Johansson, C.L. Zimmer, S. Björkander, D.H. Petursdottir, J. Dicksved, et al., Lactobacilli regulate Staphylococcus aureus 161:2-induced pro-inflammatory T-cell responses in vitro, PLoS One 8 (2013) e77893, https://doi.org/10.1371/journal.pone.0077893.
[94] C. Di Giacinto, M. Marinaro, M. Sanchez, W. Strober, M. Boirivant, Probiotics ameliorate recurrent Th1-mediated murine colitis by inducing IL-10 and IL-10-dependent TGF-beta-bearing regulatory cells, J. Immunol. 174 (2005) 3237–3246, https://doi.org/10.4049/jimmunol.174.6.3237.
[95] A. de Moreno de Leblanc, S. Del Carmen, M. Zurita-Turk, C. Santos Rocha, M. van de Guchte, V. Azevedo, et al., Importance of IL-10 modulation by probiotic microorganisms in gastrointestinal inflammatory diseases, ISRN Gastroenterol. 2011 (2011) 892971, https://doi.org/10.5402/2011/892971.
[96] S. de Roock, M. van Elk, M.E.A. van Dijk, H.M. Timmerman, G.T. Rijkers, B. J. Prakken, et al., Lactic acid bacteria differ in their ability to induce functional regulatory T cells in humans, Clin. Exp. Allergy (40) (2010) 103–110, 10.1111/j.1365-2222.2009. 03344.x.
[97] M.J. Smelt, B.J. de Haan, P.A. Bron, I. van Swam, M. Meijerink, J.M. Wells, et al., L. plantarum, L. salivarius, and L. lactis attenuate Th2 responses and increase Treg frequencies in healthy mice in a strain dependent manner, PLoS One 7 (2012) e47244, 10.1371/journal.pone.0047244 [PMC free article] [PubMed] [CrossRef] [Google Scholar].
[98] Y. Liu, N.Y. Fatheree, B.M. Dingle, D.Q. Tran, J.M. Rhoads, Lactobacillus reuteri DSM 17938 changes the frequency of Foxp3+ regulatory T cells in the intestine and mesenteric lymph node in experimental necrotizing enterocolitis, PLoS One 8 (2013) e56547, https://doi.org/10.1371/journal.pone.0056547.
[99] H. Braat, J. van den Brande, E. van Tol, D. Hommes, M. Peppelenbosch, S. van Deventer, Lactobacillus rhamnosus induces peripheral hyporesponsiveness in stimulated CD4+ T cells via modulation of dendritic cell function, Am. J. Clin. Nutr. 80 (2004) 1618–1625.
[100] A.S. Zinkernagel, C. Peyssonnaux, R.S. Johnson, V. Nizet, Pharmacologic augmentation of hypoxia-inducible factor-1alpha with mimosine boosts the bactericidal capacity of phagocytes, J. Infect. Dis. 197 (2008) 214–217.
[101] J.D. Kingsley, et al., Nanotechnology: A focus on nanoparticles as a drug delivery system, J. Neuroimmun. Pharmacol. 1 (2006) 340–350.
[102] B.J. Edagwa, et al., Long-acting antituberculous therapeutic nanoparticles target macrophage endosomes, FASEB J. 28 (2014) 5071–5082.
[103] S. Xie, et al., Biodegradable nanoparticles for intracellular delivery of antimicrobial agents, J. Control Release 187 (2014) 101–117.
[104] Brown, A.N. et al. (2012) Nanoparticles functionalized with ampicillin destroy multiple-antibiotic-resistant isolates of Pseudomonas aeruginosa and Enterobacter aerogenes and methicillin-resistant Staphylococcus aureus. Am. Soc. Microbiol. XX, YYY–ZZZ.
[105] Y. Zhao, X. Jiang, Multiple strategies to activate gold nanoparticles as antibiotics, Nanoscale 5 (2013) 8340–8350.
[106] N. Shaik, et al., Interactions of pluronic block copolymers on P-gp efflux activity: experience with HIV-1, Protease Inhib. J. Pharm. Sci. 97 (2008) 5421–5433.
[107] R. Pelgrift, A. Friedman, Nanotechnology as a therapeutic tool to combat microbial resistance, Adv. Drug Deliv. Rev. 65 (2013) 1803–1815.
[108] M.L. McLaws, The relationship between hand hygiene and healthcare-associated infection: it's complicated, Infect. Drug Resist 8 (2015) 7–18.
[109] WHO Guidelines on hand hygiene in health care: first global patient safety challenge clean care is safer care. Geneva: World Health Organization; 2009. 4. Historical perspective on hand hygiene in health care Available from: https://www.ncbi.nlm.nih.gov/books/NBK144018/. Accessed February14, 2019. [Google Scholar].
[110] H. Wu, C. Moser, H.Z. Wang, N. Hoiby, Z.J. Song, Strategies for combating bacterial biofilm infections, Int J. Oral. Sci. 7 (2015) 1–7. PMID:25504208;.
[111] S.Y.C. Tong, J.S. Davis, E. Eichenberger, T.L. Holland, V.G. Fowler, Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management, Clin. Microbiol Rev. 28 (3) (2015 Jul) 603–661, cited 2024 Jan 2];.
[112] L. Suleman, D. Archer, C.A. Cochrane, S.L. Percival, Chapter ten - healthcare-associated infections and biofilms. In: Percival SL, Williams DW, Randle J, Cooper T, editors, in: S.L. Percival, D.W. Williams, J. Randle, T. Cooper (Eds.), Biofilms in Infection Prevention and Control, Boston: Academic Press, 2014, pp. 165–184 [cited 2024 Jan 7].
[113] T.L. Kane, K.E. Carothers, S.W. Lee, Virulence factor targeting of the bacterial pathogen Staphylococcus aureus for vaccine and therapeutics, Curr. Drug Targets 19 (2) (2018) 111–127, cited 2024 Jan 2];.
[114] S. Leekha, C.L. Terrell, R.S. Edson, General principles of antimicrobial therapy, Mayo Clin. Proc. [Internet] 86 (2) (2011 Feb) 156–167, cited 2024 Jan 2];.
[115] C. Manyi-Loh, S. Mamphweli, E. Meyer, A. Okoh, Antibiotic use in agriculture and its consequential resistance in environmental sources: potential public health implications, Molecules 23 (4) (2018 Mar 30) 795, cited 2024 Jan 2];.
[116] Y. Chen, Z. Liu, Z. Lin, M. Lu, Y. Fu, G. Liu, et al., The effect of Staphylococcus aureus on innate and adaptive immunity and potential immunotherapy for S. aureus-induced osteomyelitis, Front. Immunol. [Internet] 14 (2023) cited 2024 Jan 2];.
[117] H. Chen, J. Zhang, Y. He, Z. Lv, Z. Liang, J. Chen, et al., Exploring the role of Staphylococcus aureus in inflammatory diseases, Toxins (Basel) (2022 Jul 6).
[118] R. Duan, P. Wang, Rapid and simple approaches for diagnosis of Staphylococcus aureus in bloodstream infections, Pol. J. Microbiol. 71 (4) (2022 Dec 9) 481–489, cited 2024 Jan 2];.
[119] P. Dadgostar, Antimicrobial resistance: implications and costs, Infect. Drug Resist 12 (2019 Dec 20) 3903–3910, cited 2024 Jan 2];.
[120] C. Llor, L. Bjerrum, Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem, Ther. Adv. Drug Saf. 5 (6) (2014 Dec) 229–241, cited 2024 Jan 2];.
[121] A. Bear, T. Locke, S. Rowland-Jones, S. Pecetta, F. Bagnoli, T.C. Darton, The immune evasion roles of Staphylococcus aureus protein A and impact on vaccine

development, Front Cell Infect. Microbiol 13 (2023 Sep 27) 1242702 cited 2024 Jan 2];.
[122] A.S. Collins, 2008, Preventing health care–associated infections. In: Hughes R.G., editor. Patient Safety and Quality: An Evidence-Based Handbook for Nurses [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 [cited 2024 Jan 2]. (Advances in Patient Safety). Available from: http://www.ncbi.nlm.nih.gov/books/NBK2683/ .
[123] J.M. Van Seventer, N.S. Hochberg, Principles of infectious diseases: transmission, diagnosis, prevention, and control, Int. Encycl. Public Health (2017) 22–39, cited 2024 Jan 2];.
[124] Z. Sedarat, A.W. Taylor-Robinson, Biofilm formation by pathogenic bacteria: applying a Staphylococcus aureus model to appraise potential targets for therapeutic intervention, Pathogens 11 (4) (2022 Mar 23) 388, cited 2024 Jan 2];.
[125] M. Strzelec, J. Detka, P. Mieszczak, M.K. Sobocińska, M. Majka, Immunomodulation—a general review of the current state-of-the-art and new therapeutic strategies for targeting the immune system, Front. Immunol. 14 (2023) cited 2024 Jan 2];.
[126] B. Spellberg, R. Daum, Development of a vaccine against Staphylococcus aureus, Semin Immunopathol. 34 (2) (2012 Mar) 335–348, cited 2024 Jan 2];.
[127] U. Chand, P. Priyambada, P.K. Kushawaha, Staphylococcus aureus vaccine strategy: Promise and challenges, Microbiol. Res. 271 (2023 Jun 1) 127362 cited 2024 Jan 2];.
[128] K. Kharga, L. Kumar, S.K.S. Patel, Recent advances in monoclonal antibody-based approaches in the management of bacterial sepsis, Biomed. 11 (3) (2023 Mar 2) 765, cited 2024 Jan 2];.
[129] Vacca F., Sala C., Rappuoli R.. Monoclonal antibodies for bacterial pathogens: mechanisms of action and engineering approaches for enhanced effector functions. Biomedicines [Internet]. 2022 Sep [cited 2024 Jan 2];10(9):2126. Available from: https://www.mdpi.com/2227-9059/10/9/2126.