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REVIEW

Progress in Research on Macrophage Polarization Mechanisms and Targeted Therapies in *Staphylococcus aureus* Infections

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Abstract: *Staphylococcus aureus* is a clinically prevalent, Gram-positive pathogen that can cause multiple severe infections. Macrophage polarization plays a central role in host defense and inflammatory regulation, with its M1/M2 dynamic equilibrium directly determining infection outcomes. The M1 phenotype eliminates pathogens through pro-inflammatory responses in the early phase, but excessive activation readily leads to tissue damage. In contrast, the M2 phenotype suppresses inflammation and promotes healing during the repair phase, although it may become a pathogen refuge in chronic infections. Recent studies have elucidated the roles of PAMPs, virulence factors, immunometabolism, and epigenetics in regulating polarization and have explored intervention strategies involving stem cells, exosomes, nanodelivery, novel formulations, and natural medicines, offering new avenues to overcome antibiotic limitations. However, existing evidence remains confined to animal studies, and challenges related to polarization heterogeneity and clinical translation require urgent resolution. This review summarizes the mechanisms of macrophage polarization and targeted therapeutic advances in the context of *S. aureus* infection, aiming to provide insights for immune interventions against drug-resistant infections.

Keywords: *Staphylococcus aureus*, macrophage polarization, immune regulation, drug-resistant infection, targeted therapy

Introduction

Staphylococcus aureus is one of the most common Gram-positive pathogens in clinical settings, exhibiting high adaptability and significant pathogenic potential. It can cause various severe diseases such as skin and soft tissue infections, pneumonia, sepsis, and infective endocarditis, posing substantial challenges for clinical prevention and treatment.[1,2] With the prolonged inappropriate use of antimicrobial agents, coupled with the strain's capacity for frequent genetic mutations and environmental adaptation, drug-resistant variants like Methicillin-resistant *Staphylococcus aureus* (MRSA) have proliferated. This trend increasingly limits the efficacy of traditional therapeutic approaches, creating an urgent need to explore novel prevention and treatment strategies.[3] Within the host immune system, macrophage polarization serves as a pivotal component of innate defense responses, playing a critical role in infection control, inflammatory regulation, and pathological processes like tissue fibrosis.[4] Precisely modulating the transition between different macrophage phenotypes can effectively reshape the immune microenvironment and demonstrate unique advantages in anti-infective therapies, making it a focal point of research in immunology and infectious disease studies. Based on this, this paper aims to examine the interplay between macrophage polarization and *Staphylococcus aureus* infection, elucidating its mechanisms in infection initiation and progression. It further explores potential intervention strategies targeting macrophage polarization, seeking to provide theoretical support and new directions for related research and clinical applications.

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Overview of Macrophage Polarization

Macrophages are crucial effector cells of the innate immune system, performing multifaceted roles in host defense, inflammation regulation, tissue repair, and homeostasis maintenance.[5] Traditionally, researchers classify them into two classical phenotypes: M1 macrophages are induced by signals such as IFN-γ, primarily secreting TNF-α, IL-1β, and iNOS, and play a dominant role in pathogen clearance and antitumor responses.[6] M2 macrophages develop under IL-4 and IL-13 stimulation, secreting IL-10, Arg-1, and other molecules to exert anti-inflammatory effects and promote tissue repair.[7] During *Staphylococcus aureus* infection, macrophage polarization undergoes dynamic changes. During the acute phase, free-floating bacteria are recognized via Toll-like receptors (TLRs) and phagocytosed, driving M1 polarization. This releases reactive oxygen species (ROS), nitric oxide (NO), and multiple pro-inflammatory factors to eliminate pathogens;[4] Conversely, when bacteria form biofilms, they evade phagocytosis and survive intracellularly, inducing M2 conversion in macrophages. This suppresses inflammation and promotes chronic infection.[8] At different stages, M1 and M2 often exist in an antagonistic relationship: the former dominates rapid defense during the acute phase, while the latter gradually gains dominance during chronic inflammation or repair processes, though it may also facilitate immune escape[9,10] (Figure 1). However, the M1/M2

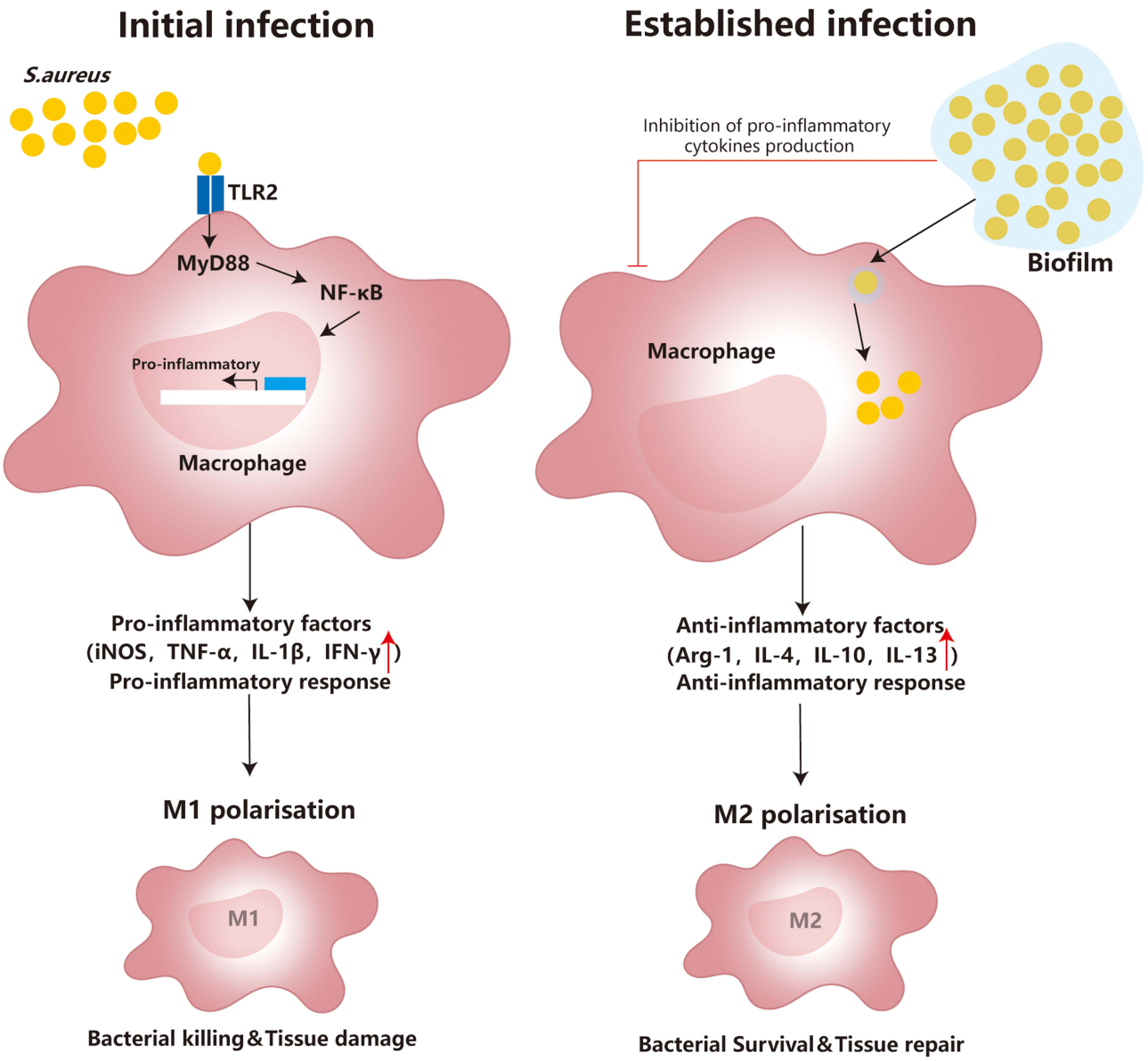

Figure 1 Overview of Macrophage Polarization.

binary classification model primarily originates from in vitro experiments and struggles to accurately reflect the dynamic state of macrophages within the complex in vivo microenvironment. Growing evidence indicates that macrophage polarization is not mutually exclusive but represents diverse functional states along a continuum. Their phenotypes can shift in response to environmental changes, often exhibiting co-expression of M1- and M2-associated molecular markers.[11] This atypical behavior is particularly pronounced in in vivo versus in vitro comparisons. Even under identical activation protocols, transcriptional profiles exhibit significant differences across distinct environments, highlighting the decisive role of the microenvironment in shaping macrophage function and phenotype.[12] Single-cell transcriptomics studies further reveal that during *Staphylococcus aureus* infection, human primary macrophages exhibit diverse and dynamic activation patterns far exceeding the traditional M1/M2 framework, demonstrating significant heterogeneity and plasticity.[13] Therefore, rather than mechanically applying a binary model, it is imperative to reassess the proper role of macrophages from functional dimensions such as "pro-inflammatory" and "anti-inflammatory/repair" within specific pathological contexts. This approach will more accurately reflect their position in the onset and progression of infection.

Key Factors Influencing Macrophage Polarization in Staphylococcus aureus Infections

Effects of Pathogen-Associated Molecular Patterns on Macrophage Polarization

During *Staphylococcus aureus* infection, pathogen-associated molecular patterns (PAMPs) serve as core signals that drive innate immune responses and shape macrophage polarization. Conservative structures on the *S. aureus* surface—including lipopeptides, peptidoglycan, lipoproteins, and nucleic acids—can be specifically recognized by pattern recognition receptors (PRRs).[8,14] Among these, Toll-like Receptor 2 (TLR2) plays a pivotal role. It activates the NF-κB canonical pathway via the adaptor protein MyD88, thereby initiating the transcription of pro-inflammatory genes and rapidly inducing the expression of M1 effector molecules such as TNF-α, IL-6, and iNOS. This establishes an innate immune response oriented toward pathogen clearance.[15,16] As an amplification mechanism for initial inflammatory signals, cytoplasmic NLRP3 inflammasomes are synergistically activated following a "dual-signal" model: The TLR2 pathway upregulates NLRP3 and pro-IL-1β (signal one), while stress signals, including ion efflux, mitochondrial ROS, and lysosomal rupture, constitute "signal two." Together, these drive caspase-1 activation, producing IL-1β and inducing Gasdermin D-mediated pyroptosis, thereby rapidly amplifying inflammatory signals.[17,18] This mechanism enhances host defense during the acute phase but, if excessively prolonged, readily causes severe tissue damage.

Notably, PAMP-induced M1 responses are not infinitely amplified but are dual-regulated by host harmful control mechanisms and the infectious microenvironment. For instance, the deubiquitinating enzyme CYLD interferes with the TRAF6/NEMO/RIPK2 signaling complex, inhibiting NF-κB activity and thereby attenuating M1 polarization.[19] Furthermore, the course of infection and local environmental factors decisively influence polarization outcomes: during the acute phase, high PAMP signaling promotes M1 dominance; whereas in chronic infections or biofilm-associated settings, signaling attenuation coupled with hypoxic and acidic conditions gradually diminishes M1 efficacy, driving cells toward M2-like phenotypes.[20]

Beyond PAMPs, multiple pore-forming toxins from *S. aureus* also serve as key drivers of M1 polarization and inflammatory amplification. Taking alpha-hemolysin (Hla) as an example, its effects exhibit a dose-dependent relationship: high concentrations of Hla form pores in macrophage membranes, leading to cell necrosis and suppression of phagocytic function; while sublethal doses impair apoptotic cell clearance by blocking Rac1-dependent actin remodeling. This causes neutrophil retention and sustained pro-inflammatory cytokine release, thereby perpetuating abnormal M1 polarization and delaying infection control.[21] In biofilm-associated environments, Hla frequently synergizes with leukocidin AB (LukAB) to induce macrophage programmed cell death, further impairing infiltration and bactericidal efficacy.[22,23] Additionally, dimeric toxins such as γ-hemolysin and Panton–Valentine leukocidin (PVL) can similarly form pores in membranes and trigger potassium efflux, thereby activating NLRP3 inflammasomes and causing excessive IL-1β release. Although these manifestations exhibit M1 pro-inflammatory characteristics, they are intrinsically associated with macrophage death, ultimately facilitating abscess wall formation that provides immune shelter for bacteria rather than adequate clearance.[24,25]

In summary, PAMPs and pore-forming toxins synergistically induce macrophage polarization toward the M1 phenotype during the acute phase of infection. PAMPs primarily facilitate rapid initiation of the inflammatory response and activate downstream signaling pathways, while pore-forming toxins enhance pro-inflammatory cascades and amplify local immune effects through cell death or sublethal injury. Concurrently, endogenous harmful regulatory mechanisms and microenvironmental changes at the infection site gradually attenuate the intensity of the M1 response and drive macrophages toward an M2-like phenotype, thereby altering the trajectory of the immune response. This dynamic equilibrium oscillating between "pro-inflammatory" and "suppressive" states reflects the host's adaptive strategy of relying on M1 macrophages for early pathogen clearance. Simultaneously, it may also create conditions conducive to subsequent immune evasion and biofilm-associated chronic infection states.

Biofilm Formation and Immune Evasion in Regulating Macrophage Polarization

During *Staphylococcus aureus* infection, biofilm formation serves as a core strategy for bacterial persistence and resistance. Its establishment is closely linked to anti-inflammatory responses and immune tolerance, constituting a key driver of chronic infection.[26] Unlike the acute phase, where pathogen-associated molecular patterns and toxins primarily drive the M1 proinflammatory response, mature biofilms progressively alter the host response through immune evasion mechanisms. This shifts macrophages toward an M2 phenotype, thereby diminishing antimicrobial efficacy and promoting chronic infection.[8] In vitro studies by Seebach et al[27] revealed that conditioned medium derived from biofilms induces elevated IL-10 expression in macrophages while decreasing the TNF-α:IL-10 ratio, suggesting the biofilm environment itself promotes macrophage shift toward the M2 functional lineage. At the molecular level, DacA—the enzyme responsible for c-DI-AMP synthesis—is highly expressed during biofilm growth. This molecule enters the extracellular matrix upon bacterial lysis, where it activates the STING-dependent pathway to induce macrophage type I interferon expression. This mechanism promotes *Staphylococcus aureus* survival within macrophages and enhances anti-inflammatory activity.[28] Alboslemy et al[29] demonstrated in vitro that conditioned medium derived from biofilms inhibits NF-κB activation and induces KLF2 upregulation, suppressing macrophage proinflammatory responses. Concurrently, Li et al[19] demonstrated that the SaeRS two-component system, during early infection, promotes bacterial aggregation and shields antigens, thereby weakening macrophage proinflammatory capacity, phagocytosis, and bactericidal functions. This establishes an immunologically low-response environment, laying the groundwork for subsequent M2-biased immune polarization.

Cell wall protein A, as one of the primary immune evasion factors, not only binds with high affinity to the Fc region of IgG to block antibody-dependent phagocytosis but also suppresses M1 phenotype maintenance at the transcriptional level via the HIF-1α/SETD2 signaling axis, further attenuating proinflammatory responses.[30] Additionally, complement inhibitory proteins such as SCIN and CHIPS can sequentially block C3 convertase and C5a receptor signaling, significantly reducing macrophage recruitment, decreasing local M1 density, and promoting conversion toward M2 or inhibitory phenotypes.[31] Collectively, *Staphylococcus aureus* biofilms attenuate M1 proinflammatory functions through multiple factors and signaling pathways while promoting macrophage M2 reprogramming, thereby sustaining immunosuppression and chronic infection. Although existing studies provide in vivo and in vitro evidence, the interplay among these factors and their clinical dominance remains unclear. Future research should integrate higher-resolution and clinically relevant studies to elucidate these mechanisms.

Effects of Metabolic Reprogramming on Macrophage Polarization

During *Staphylococcus aureus* infection, metabolic reprogramming of macrophages is widely recognized as a critical determinant of their differentiation toward pro-inflammatory or anti-inflammatory pathways. Under stimulation by PAMPs and other signals, M1 macrophages rely on aerobic glycolysis to rapidly generate ATP and provide intermediate metabolites, thereby driving the synthesis of reactive oxygen species (ROS) and nitric oxide (NO), and sustaining inflammasome activation and the continuous secretion of pro-inflammatory factors.[32,33] This metabolic profile manifests as enhanced pentose phosphate pathway activity and upregulation of the highly active isoenzyme u-PFK2, accompanied by disruption at key nodes of the tricarboxylic acid (TCA) cycle, leading to accumulation of citrate, succinate, and itaconic acid.[34] Among these, succinate stabilizes HIF-1α by inhibiting prolyl hydroxylase and promotes the expression

of glycolysis-related enzymes such as GLUT1, HK2, and LDHA, as well as IL-1β, forming a "succinate–HIF-1α–glycolysis" signaling axis that plays a central role in maintaining M1 inflammatory efficacy.[35] During M1 polarization, cells typically rely on aerobic glycolysis. This metabolic pathway rapidly generates ATP and provides metabolic intermediates, supplying energy and substrates for ROS, NO, and various pro-inflammatory factor synthesis to maximize bactericidal effects.[36] Furthermore, itaconic acid not only enhances bactericidal effects by inhibiting bacterial metabolism but also blocks succinate dehydrogenase to prevent inflammatory overactivation. However, while this action reduces tissue damage, it may also promote chronic infection.[23]

Conversely, M2 macrophages primarily rely on mitochondrial oxidative phosphorylation and fatty acid oxidation. Their characteristics include upregulation of the low-activity isoenzyme PFKB1 and the fatty acid transporter CD36, thereby enhancing triglyceride uptake and maintaining TCA cycle integrity.[37,38] Concurrently, M2 cells exhibit markedly reduced iNOS levels and upregulation of Arg-1, whose metabolites urea and ornithine further generate polyamines and proline, thereby promoting fibrosis, granuloma formation, and tissue repair.[39] In chronic infection settings, pathogen metabolites can further drive immunophenotypic shifts. For instance, lactate released from *S. aureus* biofilms inhibits HDAC11 within host cells and promotes histone H3 acetylation at the IL-10 promoter, thereby enhancing IL-10 transcription. This suppresses T cell activation and Th1 polarization, facilitating macrophage reprogramming toward an M2-like phenotype.[40] Furthermore, IL-10 downregulates glycolysis-associated enzymes via the STAT3 pathway and promotes mitochondrial oxidative phosphorylation, both of which have been shown to correlate with diminished pro-inflammatory responses in *S. aureus* meningitis and skull infection models.[41]

Recent studies reveal significant interactions between metabolism and epigenetics. For instance, methylsulfonylmethane (MSM) modulates lactate-mediated H3K18 acetylation and upregulates M2-associated gene expression, thereby promoting M2 polarization and improving outcomes in MRSA sepsis models.[32] These findings demonstrate that metabolic intermediates serve not only as energy and signaling substrates but also reshape macrophage function through epigenetic modifications. Collectively, metabolic reprogramming underpins both the host's maintenance of protective M1 function during *S. aureus* infection and the pathogen-host feedback mechanisms driving M2 conversion. However, the temporal roles of metabolic pathways during acute versus chronic infection remain poorly understood, and how metabolism and epigenetics stabilize polarized lineages within complex microenvironments is not fully elucidated. Future integration of multi-omics and in vivo dynamic tracking technologies to generate systems-level evidence will facilitate precise regulation of immune metabolism, enabling dual objectives of enhanced antimicrobial efficacy and immune homeostasis.

Macrophage Polarization Phenotypes and Outcomes of Staphylococcus aureus Infection

Dual Role of M1 Polarization: Protection and Damage

During the acute phase of *S. aureus* infection, rapid macrophage polarization toward the M1 phenotype is crucial for establishing effective antimicrobial host defense. M1 cells rely on the synergistic activation of the TLR2/MyD88/NF-κB pathway and NLRP3 inflammasome to produce large amounts of proinflammatory factors such as IL-1β and TNF-α, while releasing reactive nitrogen and oxygen species, thereby significantly enhancing phagocytosis and bactericidal capacity. This potent proinflammatory response not only rapidly reduces the pathogen burden but also recruits large numbers of neutrophils and activates adaptive immunity. Across multiple *S. aureus* infection models, maintaining M1 polarization has been demonstrated to effectively reduce bacterial counts and improve host survival rates.[8,42] However, M1 phagocytosis exhibits limitations—it is more efficient against extracellular strains but less effective against intracellular latent strains, suggesting pathogens may achieve partial immune evasion at the subcellular level.[43]

If M1-dominant inflammation lacks timely regulation, its protective effects rapidly transform into immunopathology. Sustained high levels of IL-1β, TNF-α, and ROS induce cytotoxicity, tissue necrosis, and edema, causing local injury and triggering organ dysfunction. Concurrently, excessive inflammation impedes M2 phenotype conversion, delaying inflammation resolution and tissue repair.[44] Studies reveal that *Staphylococcus aureus* vesicles (SAVs) activate TLR2 while suppressing macrophage apoptosis and phagocytic function, leading to inflammatory debris accumulation and prolonged

pathological processes. Furthermore, the m6A modifier YTHDF1 enhances M1-associated factor release by upregulating GBP4 expression, thereby exacerbating pulmonary inflammation.[45] Under prolonged M1-dominant immune conditions, T cell subset balance is disrupted, manifesting as Th17 overactivation and Treg dysfunction, ultimately causing immune dysregulation. In *S. aureus* infection models, Treg depletion reduces IL-17 levels and activates IFN-γ-dependent bacterial clearance mechanisms, suggesting Tregs play a critical role in limiting excessive inflammation.[46] In broader sepsis research, Th17/Treg imbalance has been demonstrated to correlate closely with systemic inflammatory response syndrome and organ injury risk[47] In summary, the potent proinflammatory response of M1 polarization during early infection is critical for pathogen clearance and host survival. However, without timely regulation, its persistence becomes a primary driver of immunopathology. Existing research has established the conclusive significance of the early protective effects of M1 polarization. Discoveries of novel mechanisms, such as SAVs, m6A modifications, and Th17/Treg imbalance, further reveal its potential role in inflammatory amplification and immune dysregulation. Future anti-infective strategies should focus on guiding the timely transition from M1 to M2 phenotypes after infection control, while preserving M1 antimicrobial capabilities, to achieve a dynamic equilibrium between pathogen clearance and tissue repair.

The Double-Edged Sword of M2 Polarization: Repair and Protection

During *S. aureus* infection, the polarization of macrophages toward the M2 phenotype exhibits a classic double-edged sword effect, with its beneficial and detrimental roles primarily determined by the timing and sustained intensity of polarization. During the acute inflammatory resolution phase, M2 macrophages effectively suppress sustained proinflammatory pathway activation by secreting IL-10, TGF-β, and Arg-1. This prevents secondary tissue damage while promoting fibroblast activation and angiogenesis, thereby accelerating wound healing and restoring homeostasis.[48] Research on metabolic and immune regulation further indicates that M2 function relies on metabolic pathways such as oxidative phosphorylation and fatty acid oxidation to sustain long-term reparative effects. In MRSA skin and soft tissue infection models, myeloid cell glucose transporter GLUT1 was demonstrated to promote macrophage anti-inflammatory polarization via a PPARγ-dependent mechanism, thereby shortening the infection cycle and improving host prognosis.[48] Moreover, specialized pro-resolving mediators (SPMs), such as resolvins and mareins, enhance apoptotic cell clearance and promote anti-inflammatory factor expression. In infection contexts, they are recognized as key mechanisms limiting immunopathology and driving tissue repair.[49,50] This evidence underscores the decisive role of timely M2 polarization in inflammation resolution and tissue reconstruction.

However, when the M2 phenotype is excessively activated or persistently maintained during early infection, its anti-inflammatory characteristics may compromise antimicrobial efficacy and provide immune shelter for pathogens. Under such circumstances, macrophage phagocytic and bactericidal functions decline, while monocyte and neutrophil recruitment becomes restricted. This progressively establishes a low-inflammation, high-tolerance microenvironment locally, thereby increasing the risk of bacterial colonization, chronic infection, and recurrence.[4,51] Both clinical and animal studies indicate that in chronic infections and biofilm-associated lesions, an M2-biased immune environment is closely associated with prolonged bacterial survival and delayed wound healing. Peng et al demonstrated in an implant infection model that *S. aureus* biofilms induce the proliferation of mesenchymal stem cells (MSCs) and drive their M2-type differentiation, thereby enhancing immunosuppression and providing sustained shelter for bacteria[52,53] Furthermore, in a mouse skin abscess model, Thurlow et al confirmed that biofilm infection similarly drives M2 polarization, compromising the abscess wall's effective inflammatory barrier and thereby creating favorable conditions for sustained bacterial survival and chronicity.[54] Recent studies further reveal that impaired macrophage phagocytic clearance leads to localized accumulation of necrotic debris, which not only impedes repair processes but may also perpetuate chronic infection.[44]

In summary, M2 polarization in *S. aureus* infection functions both as a "repair promoter" and potentially as a "pathogen protector." Its effects are highly dependent on the timing and intensity of induction: during the inflammatory resolution phase, M2 functions generally help limit immunopathology and promote repair; however, in the early or chronic stages of infection, excessive M2 bias may lead to persistent pathogen presence and increased recurrence risk. Future research should focus on precisely regulating the timing and intensity of M2 polarization to avoid its overactivation in the early or chronic phases of infection, thereby enhancing antimicrobial efficacy and reducing immune escape.

Emerging Therapeutic Strategies Targeting Macrophage Polarization in Staphylococcus aureus Infections

Macrophage polarization plays a pivotal role in host defense and tissue repair during *Staphylococcus aureus* infection. Accordingly, modulation of polarization has become a major focus in the development of novel anti-infective therapies. With advances in immunometabolism, biomaterials, and modern pharmacology of traditional medicines, multiple emerging strategies have been proposed, including stem cell and exosome therapy, nanoparticle-based delivery systems, biologics and cell engineering, and natural or compound formulations. These approaches remodel the host immune microenvironment, promote inflammation resolution, or enhance antimicrobial activity, thereby offering new insights into the treatment of drug-resistant infections. (The representative therapeutic strategies targeting macrophage polarization in *S. aureus* infections are summarized in Table 1).

Table 1 Representative Therapeutic Strategies Targeting Macrophage Polarization in *Staphylococcus Aureus* and MRSA Infections

Treatment Strategy Categories	Representative Intervention System	Experimental Model	Regulatory Mechanism	References
Stem Cell and Exosome Therapy	BM-MSC CM	Murine MRSA skin wound model	MSC secretome reduces inflammation and increases macrophage infiltration to promote healing	[55]
	AD-MSC Sec.	In vitro MRSA infection	Secretome shows antibacterial activity and immunomodulatory potential	[56]
	Eq-MSC CM	Equine MRSA skin wound model	Enhances macrophage infiltration but polarization not quantified	[57]
	hAD-MSC LL-37	In vitro *S. aureus* model	Exerts antibacterial and immunomodulatory effects via LL-37	[58]
Nano particle and Smart Delivery Systems	Fe_3O_4@PDA-Ag	Murine MRSA skin infection model	Promotes M1 polarization to enhance bactericidal activity and, via synergistic photothermal/redox effects, disrupts bacteria.	[59]
	CA/IFN-γ LPHN	Intramacrophage MRSA infection model	Deliver IFN-γ to drive M1 polarization and eliminate persister bacteria.	[60]
	MSN	Implant-associated *S. aureus* infection model	Coordinate macrophage repolarization and pyroptosis to improve infection control.	[61]
	rGB/QCS/PDA-PAM	Murine MRSA wound model	Mitigates excessive M1-driven inflammation and promotes tissue repair.	[62]
	DG-CDs	Murine MRSA keratitis model	Suppress pro-inflammatory M1 responses and promote M2 polarization to correct immune imbalance.	[63]
	AA-CDots	MRSA pneumonia model	Inhibit the PI3K/AKT/mTOR pathway, thereby enhancing M1 polarization and bactericidal responses.	[64]
	Fu-Zn-MOF microneedle	Murine MRSA wound infection	Fosters M2 polarization and accelerates wound healing.	[65]
	ZnO_2@CeMOF/Br	MRSA biofilm infection model	Activates M1 polarization, boosts phagocytosis, and disrupts bacterial biofilms.	[66]
	ΔagrA-AMV-VAN	Murine MRSA peritonitis model	Induce M1 polarization and enhance intracellular killing, targeting the agrA pathway.	[67]
	MΦ-NDs	Murine systemic MRSA infection	Receptor-mediated recognition and phagocytosis strengthen M1 bactericidal activity while easing inflammation.	[68]

(*Continued*)

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Table 1 (Continued).

Treatment Strategy Categories	Representative Intervention System	Experimental Model	Regulatory Mechanism	References
Novel Biologics and Cell Engineering	RvD1 / RvD5	*S. aureus* infection	Promote M2 polarization, enhance efferocytosis, accelerate inflammation resolution	[69]
	MEK1/2 inhibitor	MRSA USA300 murine model	Suppress M1-dominant inflammation, restore immune balance without affecting bacterial clearance	[70]
	PPNs	MRSA wound biofilm model	Lyse bacterial biofilms and induce macrophage transition from the M1 to the M2 phenotype.	[71]
	CAR-MΦ	Implant-associated *S. aureus* infection	Generate antibacterial, immunoregulatory CAR-MΦ to enhance clearance and osseointegration	[72]
	mRNA-LNP CAR-MΦ	MRSA sepsis model	In vivo engineered CAR-MΦ improve MRSA clearance and host survival	[73]
Natural Products and Compound Formulations	Ru–Quercetin, Baicalein, Baicalin	MRSA-infected wound and murine skin infection models	Suppress virulence and inflammation, remodel macrophage phenotype, and improve wound healing	[74,75]
	Berberine	MRSA skin infection and clinical isolate infection models	Inhibit NF-κB pathway, downregulate IL-6/TNF-α, promote M2 polarization and antibiotic sensitivity	[76]
	Esculin / Esculetin	MRSA induced acute lung injury and murine sepsis models	Activate Nrf2–ARE pathway, inhibit TLR2–MyD88–NF-κB signaling, restore M1/M2 metabolic balance, promote M2 polarization	[77]
	HMOs	Human macrophage in vitro *S. aureus* infection model	Modulate macrophage phenotype and effector function (some structures enhance M1-like activation) to optimize antibacterial immunity	[78]
	Bufei Jiedu Formula	Murine persistent MRSA infection model	Activate CD40 signaling, promote M1 polarization and M2 to M1 repolarization, and reduce persistent bacterial burden.	[79]
	Sanhuang Ointment	MRSA skin soft-tissue infection model	Inhibit IL-17/NF-κB pathway, suppress pro-inflammatory cytokines, enhance macrophage phagocytosis and M2 polarization	[80]

Stem Cell and Exosome Therapy

MSCs demonstrate broad application prospects in regenerative medicine and infectious disease treatment due to their multipotent differentiation potential and immunomodulatory properties. Recent studies indicate that MSCs and their secreted exosomes play a pivotal role in intervening *Staphylococcus aureus* infections by regulating macrophage polarization.[55,81] MSCs remodel the local immune environment through paracrine mechanisms, inducing M1-to-M2 macrophage conversion to suppress excessive inflammation and promote tissue repair. In a mouse model of MRSA infection, the secretome of bone marrow-derived MSCs significantly reduced bacterial load at the wound site and accelerated healing, while also enhancing macrophage infiltration and functional regulation.[55] Secretions from adipose-derived MSCs have also been demonstrated to exert direct inhibitory effects on clinically isolated strains, including MRSA, offering new insights for developing cell-free therapies based on MSCs.[56] The key effects of MSCs primarily rely on exosomes. These vesicles, as crucial carriers for intercellular communication, can load and deliver various bioactive molecules, including regulatory microRNAs.[82] Some exosomes suppress M1 inflammatory responses by downregulating the MyD88/STAT1 pathway while enhancing CD73-dependent adenosine signaling, thereby promoting M2 polarization and achieving anti-inflammatory and reparative functions.[83,84] However, most evidence originates from sepsis or acute lung injury models, with limited direct validation in *S. aureus* infection contexts. Their clinical utility requires further investigation. Notably, *S. aureus* itself releases bacterial extracellular vesicles that may interfere with macrophage clearance of apoptotic cells and delay wound healing.[44] Therefore, when developing MSC-exosome-related therapies, the disruptive effects of pathogen-derived vesicles must be fully considered to avoid adverse impacts on host

immune regulation. This not only imposes higher demands on exosome purification and quality control but also underscores the necessity of strictly adhering to GMP standards in future clinical translation to ensure the safety and efficacy of MSC-exosome formulations.

Nano Particle and Smart Delivery Systems

In treating MRSA infections, traditional antibiotics often face efficacy limitations due to poor drug penetration or the presence of biofilm barriers. In recent years, nanoparticle and smart delivery systems have emerged as novel research avenues by integrating antimicrobial and immune-modulating functions to overcome this bottleneck. Some studies utilize characteristics of the infectious microenvironment (acidic pH, reactive oxygen species accumulation, bacterial secreted enzymes, etc.) as trigger signals to construct responsive nanoplatforms. In MRSA infection models,[59] such systems release antimicrobial drugs during the early inflammatory phase to enhance M1 polarization and bactericidal efficacy, then switch to releasing pro-repair molecules during the repair phase to promote M2 polarization and tissue healing, thereby balancing pathogen clearance with tissue protection. For intracellularly retained MRSA, lipid-polymer hybrid nanoparticles were developed to co-deliver antibiotics and IFN-γ into infected macrophages. This strategy not only improved intracellular drug delivery efficiency but also significantly enhanced bactericidal capacity by activating host antimicrobial pathways, demonstrating the potential of nanoplatforms in immune reprogramming.[85] In implant-associated infection research, nanostructured surface modifications of materials also exhibit immunomodulatory effects. For instance, peptide-modified mesoporous silica nanoparticles suppress excessive NLRP3 inflammasome activation while upregulating IL-10 and Arg-1 expression, thereby promoting M2 polarization and improving implant integration outcomes.[61] Furthermore, photothermal/photodynamic composite hydrogels effectively inactivate MRSA at lower temperatures while suppressing excessive M1 responses by improving the local inflammatory environment, thereby reducing secondary damage and promoting subsequent repair.[62] In recent years, with the rise of drug-resistant strains, immunomodulatory strategies based on nanotechnology have garnered significant attention in infection treatment. Novel nanomaterials such as carbon dots (CDs) and metal–organic frameworks (MOFs) exhibit excellent biocompatibility and antibacterial activity, and achieve dual effects of antibacterial action and immune regulation by targeting macrophage polarisation. Studies indicate that guanidinated dextran-conjugated carbon dots (DG-CDs) suppress biofilm formation in MRSA infection models while improving immune imbalance and tissue repair by inhibiting M1 proinflammatory responses and promoting M2 polarisation.[86] Carbon dots (CDots) synthesised from ascorbic acid and polyethyleneimine bind to the PI3K catalytic subunit PIK3CD, inhibiting the PI3K/AKT/mTOR pathway. This enhances M1 polarisation, boosts macrophage bactericidal capacity, and significantly ameliorates MRSA-induced pulmonary infection.[64] Beyond carbon dots, MOF-based nanosystems also demonstrate promising anti-infective potential. ZIF-8@Fu nanoparticles loaded with low-molecular-weight fucoidan and coated with hyaluronic acid sustainably release Zn^2+ and Fu, promoting macrophage M1-to-M2 conversion, reducing inflammation, and accelerating repair.[65] While ZnO_2@CeMOF/Br nanocatalysts release hydrogen peroxide and hypochlorous acid in acidic environments, disrupting MRSA biofilms and inducing M1 polarisation to enhance phagocytosis and bactericidal responses.[66] Carbon dots and MOF materials achieve synergistic antibacterial and immunomodulatory effects by modulating macrophage polarisation through nanostructure engineering, offering novel non-antibiotic therapeutic avenues for MRSA infections.

In summary, novel nanomaterials such as carbon dots and metal-organic frameworks offer innovative approaches to modulating macrophage polarisation and achieving antibacterial-immune balance. These materials enhance host immune defence while reducing antibiotic resistance risks, combining targeting capabilities with biocompatibility, demonstrating significant potential for non-antibiotic anti-infection strategies. Future research should further focus on elucidating its mechanism of action, in vivo safety, and clinical translational assessment to advance the application of nano-immunomodulatory materials in MRSA and other drug-resistant bacterial infections.

Novel Biologics and Cell Engineering

The rapid advancement of novel biologics and cell engineering technologies has opened new avenues for improving outcomes of *S. aureus* infections by modulating macrophage polarization. Among biologics, host-derived SPMs have

garnered significant attention.[49] Studies indicate that α-hemolysin induces M2-like macrophages to synthesize SPMs and activate pathways related to inflammation resolution and repair. Under exogenous supplementation, molecules such as resolvins and maresins further enhance apoptotic cell clearance and anti-inflammatory factor expression. Animal experiments have confirmed their ability to accelerate wound healing significantly.[49,50] Furthermore, the NLRP3 inflammasome emerges as a potential therapeutic target for pathologies characterized by excessive inflammatory amplification. Studies demonstrate that the specific inhibitor MCC950 significantly reduces NLRP3-dependent inflammatory responses in macrophage models infected with *S. aureus*, while enhancing antimicrobial efficacy.[87] In cellular engineering, chimeric antigen receptor macrophages (CAR-M) have been employed to improve pathogen recognition and phagocytic capacity. Animal studies indicate that this strategy effectively reduces bacterial load in abscess models while maintaining the M1/M2 balance through precise regulation of the signaling pathway, thereby preventing excessive immune activation.[88,89] Concurrently, novel applications integrating phage therapy with materials science show promise. For instance, phage-polymer composites not only demonstrated the ability to disrupt MRSA biofilms in animal models but were also associated with reduced local inflammation and restoration of the M2 reparative phenotype, offering a novel intervention for infection treatment.[71] In recent years, synthetic small molecules have demonstrated significant potential in regulating macrophage polarisation and improving *Staphylococcus aureus* infections. Studies indicate that sulforaphane (SFN) alleviates proinflammatory responses and apoptosis by inhibiting the p38/JNK MAPK signalling pathway and downregulating miR-142-5p and miR-146a-5p. This reduces expression of M1 markers (such as iNOS, IL-1β, IL-6, TNF-α), significantly inhibiting *S. aureus* survival within macrophages. This suggests SFN may restore immune homeostasis by regulating polarisation.[90] Furthermore, the MEK1/2 inhibitor PD0325901 demonstrated anti-inflammatory advantages in a MRSA (USA300)-infected mouse model. It reduced proinflammatory factor release from macrophages and mitigated neutrophil-mediated inflammation without compromising bacterial clearance capacity.[70] Collectively, novel interventions such as synthetic small molecules, biologics, and cell engineering offer multi-tiered strategies for modulating macrophage polarisation and improving outcomes in drug-resistant bacterial infections. These approaches can simultaneously suppress inflammatory responses and promote immune reconstitution, achieving dual effects of antimicrobial activity and tissue repair. Although demonstrating significant potential in experimental studies, their stability, specificity, and safety within complex infectious microenvironments require further validation. Future efforts should focus on mechanism optimization and translational research to advance their clinical application.

Natural Products and Compound Formulations

Natural products and compound formulations, owing to their multi-target actions and relatively low toxicity, represent a significant resource pool for regulating macrophage polarization.[91,92] Among individual compounds, flavonoids have been most extensively studied. For instance, quercetin-loaded nanomedicines effectively suppressed excessive M1 responses and promoted M2 polarization in infected wound models, thereby accelerating tissue repair.[74] Baicalin and its glycosides reduce inflammation in *S. aureus*-infected animal models by modulating the NF-κB and STAT pathways, while promoting angiogenesis and collagen deposition, providing experimental support for the modern pharmacological application of traditional Chinese medicine monomers.[93,94] Berberine exhibits dual effects: it directly inhibits bacteria and enhances antibiotic sensitivity, while indirectly promoting M2 phenotype conversion by suppressing the release of proinflammatory factors, thereby improving the immune and repair environment at infected wounds.[76,86] Additionally, specific nutrition-related molecules hold potential value. For instance, human milk oligosaccharides (HMOs) regulate the response patterns of human macrophages in vitro and enhance the secretion of anti-inflammatory factors, suggesting their potential application in immune protection against chronic infections and in susceptible populations, such as infants and young children.[78]

Compound formulations exhibit more substantial synergistic effects in immune regulation due to interactions among their components. The Lung-Nourishing and Toxin-Clearing Formula significantly improved treatment outcomes in MRSA persistent infection models by regulating the distribution of macrophage phenotypes, enhancing CD40 expression, and promoting the conversion from M1 to M2, thereby balancing pathogen clearance and tissue protection.[79] As a traditional topical compound, Sanhuang Ointment has been demonstrated in models of infectious skin wounds and

MRSA to downregulate the IL-17/NF-κB pathway, mitigate inflammatory damage, and improve histopathological outcomes. Although direct evidence for its regulation of macrophage polarization is lacking, experimental observations suggest that it enhances macrophage phagocytic function and reduces levels of proinflammatory factors. This suggests it may indirectly suppress M1 responses and promote M2 phenotype upregulation.[80] Beyond plant extracts and compound formulations, specific metabolites derived from natural fermentation processes have also demonstrated novel research value in regulating macrophage polarisation and infectious inflammation. Studies indicate that esculin, a metabolite from the sauerkraut fermentation bacterium Bacillus safensis SK14, modulates immune responses via the gut-lung axis in an MRSA-induced acute lung injury model. It inhibits the TLR2-MyD88-NF-κB pathway while activating the Nrf2-ARE signalling pathway, thereby reducing M1 polarisation, promoting M2 polarisation, alleviating inflammation, and enhancing antioxidant capacity.[77] Additionally, esculetin (ELT) demonstrated significant anti-inflammatory effects in a sepsis-induced acute lung injury model by achieving metabolic reprogramming through inhibiting M1 glycolytic metabolism and promoting M2 fatty acid β-oxidation, thereby correcting macrophage polarisation imbalance.[95] Synthesising current research findings, natural metabolites primarily achieve fine-tuned regulation of macrophage polarisation by modulating energy metabolism and signalling networks. These compounds suppress M1 proinflammatory responses while promoting M2 reparative phenotypes, alleviating infectious inflammation and tissue injury. This offers novel insights for non-antibiotic immune interventions. Although multiple animal studies have validated their immunomodulatory potential, existing research suffers from insufficient mechanistic elucidation, unclear target identification, and a lack of clinical validation. Future studies should focus on elucidating the coupling mechanisms between their structural characteristics and metabolic reprogramming effects, while assessing their safety and translational value at the systems immunology and multi-omics levels to advance the application of natural metabolites in the prevention and treatment of drug-resistant bacterial infections.[96]

Summary and Outlook

In summary, macrophage polarisation plays a central regulatory role in the immune response to *Staphylococcus aureus* infection. M1 macrophages eliminate pathogens during the acute phase by inducing inflammatory responses, while M2 macrophages promote inflammation resolution and tissue repair during recovery. The dynamic equilibrium between these two types collectively determines infection progression and host prognosis. In recent years, pathogen-associated molecular patterns, virulence factors, and immunometabolism have been demonstrated to play crucial roles in polarisation regulation. This has spurred diverse intervention strategies across fields such as stem cell exosomes, nanomedicines, synthetic small molecules, and traditional Chinese medicine formulations, offering new avenues to overcome antibiotic resistance limitations.

Despite significant research advances, challenges persist, including complex mechanisms, limited model diversity, and constrained clinical translation. The current M1/M2 dichotomy inadequately reflects macrophage heterogeneity within the infectious microenvironment, with their phenotypic plasticity and regulatory networks requiring further elucidation. The interplay between energy metabolism and epigenetic regulation remains unclear, necessitating enhanced identification of key metabolic nodes and druggable targets. Novel delivery systems such as nanocarriers, exosomes, and CAR-M cells show promise in immune regulation, but their targeting precision, stability, and immunological safety require systematic optimisation. Future research should integrate single-cell sequencing and spatial omics technologies to map the differentiation trajectories of macrophage lineages during infection and identify core molecules regulating metabolism and signalling. Concurrently, refining efficacy and safety evaluation systems will promote integrating traditional Chinese medicine formulas with modern formulation technologies, thereby advancing the clinical translation of experimental findings. Overall, future efforts should transition from single-mechanism analysis to systematic intervention optimisation, achieving synergistic immune regulation and antimicrobial therapy to provide theoretical foundations and technical support for precision prevention and treatment of MRSA infections.

The abbreviations used throughout this article are listed in Table 2.

Table 2 Abbreviations

Abbreviation	Full Term
AA-CDots	Amino acid–modified carbon dots
AD-MSC Sec.	Adipose-derived mesenchymal stem cell secretome
AGR / ΔagrA	Accessory gene regulator A (mutant ΔagrA)
Arg-1	Arginase-1
ATP	Adenosine triphosphate
BM-MSC CM	Bone marrow-derived mesenchymal stem cell conditioned medium
CAR-MΦ / CAR-M	Chimeric antigen receptor–engineered macrophage
CA/IFN-γ LPHN	Cationic antibiotic/Interferon-γ lipid–polymer hybrid nanoparticle
CD36	Cluster of differentiation 36
CD40	Cluster of differentiation 40
CHIPS	Chemotaxis inhibitory protein of *Staphylococcus aureus*
c-DI-AMP	Cyclic di-adenosine monophosphate
CYLD	Cylindromatosis
DG-CDs	Dextran-guanidinated carbon dots
DAMPs	Damage-associated molecular patterns
ELT	Esculetin
Eq-MSC CM	Equine mesenchymal stem cell conditioned medium
FAO	Fatty acid oxidation
Fe_3O_4@PDA-Ag	Fe_3O_4@polydopamine–silver composite
Fu-Zn-MOF	Fucoidan-loaded zinc metal–organic framework
GBP4	Guanylate-binding protein 4
GLUT1	Glucose transporter 1
GSDMD	Gasdermin D
HDAC11	Histone deacetylase 11
HIF-1α	Hypoxia-inducible factor-1 alpha
HMOs	Human milk oligosaccharides
Hla	Alpha-hemolysin
IFN-γ	Interferon-gamma
IL-1β, IL-6, IL-10, IL-17	Interleukin-1β, −6, −10, −17
iNOS	Inducible nitric oxide synthase
IRF3	Interferon regulatory factor 3
KLF2	Krüppel-like factor 2
LDHA	Lactate dehydrogenase A

(*Continued*)

Table 2 (Continued).

Abbreviation	Full Term
LukAB / PVL	Leukocidin AB / Panton–Valentine leukocidin
MAPK / p38 / JNK / ERK	Mitogen-activated protein kinase pathway members
MEK1/2	MAPK/ERK kinase 1/2
MOF	Metal–organic framework
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSCs	Mesenchymal stem cells
MSM	Methylsulfonylmethane
MyD88	Myeloid differentiation primary response 88
NF-κB	Nuclear factor κ-light-chain-enhancer of activated B cells
NEMO	NF-κB essential modulator
NLRP3	NOD-like receptor family pyrin domain-containing 3
NO / ROS	Nitric oxide / Reactive oxygen species
Nrf2–ARE	Nuclear factor erythroid-2-related factor 2–antioxidant response element pathway
OXPHOS	Oxidative phosphorylation
PAMPs	Pathogen-associated molecular patterns
PFKB1 / u-PFK2	6-Phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1 (isoenzyme u-PFK2)
PI3K/AKT/mTOR	Phosphoinositide 3-kinase / Protein kinase B / Mammalian target of rapamycin
PPNs	Polymeric porous nanospheres / Photothermal porous nanostructures
PPP	Pentose phosphate pathway
PRRs	Pattern-recognition receptors
RvD1 / RvD5	Resolvin D1 / Resolvin D5
SaeRS	*Staphylococcus aureus* exoprotein regulatory system
SCIN	Staphylococcal complement inhibitor
SETD2	SET domain-containing 2
SFN	Sulforaphane
SPMs	Specialized pro-resolving mediators
STAT3	Signal transducer and activator of transcription 3
STING	Stimulator of interferon genes
TCA	Tricarboxylic acid cycle
TGF-β	Transforming growth factor-beta
Th17 / Treg	T helper 17 / Regulatory T cells
TLR / TLR2 / TLR4	Toll-like receptor 2 / 4
TNF-α	Tumor necrosis factor-alpha

(*Continued*)

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Table 2 (Continued).

Abbreviation	Full Term
USA300	Community-associated MRSA lineage
YTHDF1	YTH N6-methyladenosine RNA-binding protein 1
ZnO_2@CeMOF/Br	Zinc peroxide@cerium-based metal–organic framework/bromide composite

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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