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Material-based treatment strategies against intraosseous implant biofilm infection

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ABSTRACT

Implant-associated infections present a significant clinical obstacle for orthopedic practitioners, with bacterial biofilm formation serving as a pivotal factor in the initiation, progression, and management of such infections. Conventional approaches have proven inadequate in fully eradicating biofilm-related infections. Consequently, novel material-based therapeutic strategies have been developed, encompassing the utilization of antimicrobial agents, delivery vehicles, and synergistic antibacterial systems. In this review, we provide a succinct overview of recent advancements in anti-biofilm strategies, with the aim of offering insights that may aid in the treatment of intraosseous implant infections.

1. Introduction

The prevention and treatment of infectious diseases have long been a prominent challenge in the field of clinical medicine, with over 80 % of infections being closely linked to the formation of bacterial biofilms [1–3]. In the mid-1970s, basic studies on dental plaque by Gibbons and Van Houte laid the foundation for the role of bacterial biofilms in both health and disease [4]. Subsequently, from 1980 to 1990, Costerton systematically developed theories on bacterial biofilms, positing that biofilms are intricate, multicellular membranes created by bacteria on tissue and organ surfaces. Bacteria do not typically develop bacterial biofilms in circulating bodily fluids, but they are capable of forming bacterial biofilms on inanimate surfaces, such as artificial joints and heart valves [5–8]. The United States experiences approximately 17 million biofilm-related cases annually, resulting in a direct economic burden of approximately $90 billion, with orthopedic implant infections being the most significant contributor to this cost [9,10]. Recent research indicates that the prevalence of postoperative infection following fracture surgery ranges from 0.4 % to 16 %, with open fractures accounting for 1.5 % of cases [11,12]. Additionally, the infection rate for artificial joint replacements falls between 1.2 % and 2.2 %, while pelvic and tibial tumor prosthesis reconstructions have infection rates as high as 15 %–43 % [13]. The prevalent bacteria responsible for infections, namely *Staphylococcus aureus* and *Staphylococcus epidermidis,* exhibit a pronounced propensity to adhere to orthopedic implants [14]. Consequently, even a minimal bacterial presence can result in bacterial biofilms and protect themselves from antibiotics [1,9,10], rendering the eradication of biofilm on orthopedic implants challenging with ordinary therapy (see Table 1).

The presence of bacterial biofilms and the development of adaptive metabolic changes present significant challenges in the treatment of orthopedic implant-related infections. Current treatment options for these infections include DAIR (Debridement, Antibiotics, and Implant Retention), one-stage revision (complete removal and replacement of the infected implant in a single surgery), and two-stage revision (initial implant removal, followed by long-term antibiotic therapy and subsequent implant replacement). Nevertheless, the aforementioned treatment approaches exhibit notable rates of failure (DAIR, 30%–40 % [15–18]; one-stage, 15%–20 % [19,20]; two-stage, 5%–15 % [21–23]), particularly in cases of complex infections and those stemming from drug-resistant pathogens, posing challenges in effective management. Consequently, there is a pressing need for innovative therapeutic and preventive measures to mitigate these challenges. Of the various treatment modalities available, antibacterial strategies centered on material enhancement and refinement are currently receiving heightened research attention and offer greater potential for practical application. Scholars are currently investigating enhanced strategies for combating bacterial biofilms infections through the incorporation of physical,

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chemical, and biological antibacterial agents. The manipulation of surface morphology on implants can effectively modify the structure and chemical composition of the implant surface, thereby impeding bacterial adhesion and proliferation, ultimately diminishing the likelihood of infection. Biomaterial-targeted therapy employs strategies, such as the use of nanoparticles and carriers, to facilitate the targeted delivery of antibiotics to the infection site, thereby augmenting local antibiotic concentrations, mitigating systemic toxicity and adverse effects, and ultimately improving treatment efficacy. The utilization of immune activation and reconstruction therapy in conjunction with biomaterial design has the potential to modulate the host immune response, thereby bolstering the body's ability to combat infections. These innovative approaches offer a promising avenue for enhancing the efficacy and preventative measures associated with orthopedic implant-related infections, ultimately reducing the likelihood of treatment failures and complications. By integrating novel methodologies in the realms of physical, chemical, and host immune responses, we can enhance our ability to tackle the complexities associated with orthopedic implant-related infections.

2. The characteristics of bacterial biofilms

Bacteria adhere to contact surfaces, secrete polysaccharide matrix, fibrin, lipid-protein, etc., and envelop themselves to create a membrane composed of numerous aggregations [24]. The bacterial biofilms exhibit the following characteristics: 1) complexity in structure, as they are formed by a diverse array of microorganisms and host cells, featuring varying colony structures, matrices, polysaccharides, and proteins; 2) resistance to antibiotics, with bacteria within biofilms frequently demonstrating heightened resistance due to the stability and enhanced defense mechanisms of the bacterial community within the biofilm; 3) The challenge of removing biofilms arises from the protective layer formed by the interaction between bacteria and the polysaccharide matrix, which can resist conventional cleaning and disinfection methods; 4) Biofilms frequently contribute to the development of chronic infections, resulting in persistent and challenging-to-treat diseases; 5) The presence of bacteria and matrix substances within biofilms can activate the host immune system, leading to the secretion of elevated levels of inflammatory mediators, including tumor necrosis factor and interleukins, thereby aggravating the pathological state.

At the macro level, the formation of biofilm involves a complex dynamic process that can be categorized into five stages: reversible attachment, irreversible attachment, microcolony formation, biofilm maturation, and cellular detachment. During the reversible attachment stage, bacteria nonspecifically attach to the substrate surface. In the irreversible attachment stage, bacteria interact with substrate surfaces through proteins or adhesins. The microcolony formation stage involves bacteria producing extracellular polymer microcolonies. In the biofilm maturation stage, bacteria synthesize and release signal molecules. Finally, in the cellular detachment stage, bacteria leave the biofilm and return to an independent planktonic lifestyle [25–27]. During the dynamic process of bacterial interaction with surrounding tissue cells, the presence of bacteria triggers the secretion of fibrin and other antibacterial substances to restrict bacterial spread. However, the introduction of implants disrupts the equilibrium of the local immune microenvironment, resulting in incomplete eradication of bacteria [10,28,29]. This phenomenon is attributed to the formation of a protective barrier by adhesion proteins, polysaccharides, and cellulose secreted by bacteria and tissues, which enables bacteria to evade immune elimination [5,30]. Research conducted on animal models has demonstrated that the presence of foreign bodies can significantly lower the concentration of bacteria needed to cause infection by over 100,000-fold [31]. Additionally, interactions between neutrophils and implants can lead to neutrophil dysfunction, thereby increasing susceptibility to infection [32].

At the microscopic scale, prolonged interactions between bacteria within a biofilm and the immune system result in adaptive changes, including group behaviors and drug-resistant mutations, that confer resistance to antibiotics and immune responses. Studies indicate that the bacterial quorum sensing system regulates biofilm formation, and disrupting this system can prevent the development of mature biofilms, thereby reducing resistance to sterilizing agents [33–35]. Following the formation of biofilms by bacteria, there is an upregulation of proteins and genes associated with adhesion and invasion, including polysaccharide intercellular adhesin (PIA) [36,37] and outer membrane proteins (OMPs) [38–40], which further strengthen the barrier effect of the biofilm. The PIA protein, produced by bacteria such as *Staphylococcus* epidermidis, is an intracellular adhesive polysaccharide that facilitates colony formation and contributes to the structure of bacterial biofilms. The icaADBC gene cluster plays a crucial role in the synthesis and transportation of PIA [41–43]. Within this cluster, genes icaA and icaD are responsible for encoding the core enzyme and regulatory

Table
Current material-based therapeutic strategies for BBF infection.

Strategy	Methods and principles	Application	Advantages	References
Prevent biofilm formation (inhibit nonspecific adhesion of bacteria)	Modification of surface morphology of materials Adjust the roughness & Morphological mode The threshold depends on the type of bacteria The spacing of the three-dimensional structure is smaller than the size of the bacteria Change the surface charge of the material	Pinpoint matrix pattern; cone array Zwitterionic polymers, such as pAAZ; surface finishing materials that integrate different charge componentss	Kill bacteria or avoid the adherence of bacteria directly Can also be used as an antibiotic carrier to improve the penetration ability of drugs.	[56] [59–61] [63–69]
To destroy the biofilm structure.	Biofilm is disintegrated by physicochemical and other methods Antibiotic synergy Non-antibiotic-dependent targets	Exogenous heat and endogenous production of reactive oxygen species (ROS), such as photothermal therapy (PTT), photodynamic therapy (PDT), chemodynamic therapy (CDT), Sonodynamic Therapy (SDT) Interferes with cellular energy metabolism, include $Cu2^{+}$, Ag^{+}, Fe^{3+}, Selenium and sulfur; trigger iron or copper death.	Promote immune infiltration while addressing issues such as insufficient sterilization, low drug permeability, and cytotoxicity Low risk of inflammatory damage and cytotoxicity	[72–81] [83] [84,86,89]
Immune reactivation and reconstitution	Induces intracellular iron or copper overload Targeted delivery of reactive oxygen species	Copper polyoxymetalate clusters (Cu-POM) combined with PTT	Interfere with the energy circulation and metabolism of bacteria Antibacterial effects throughout all stages Long -lasting sterilization	[89,100,101] [102]

factors essential for the synthesis of PIA, while genes icaB and icaC encode components of the PIA transport complex. Deletion of these genes has been shown to impede the formation of biofilms. OMPs encompass a diverse array of proteins that facilitate adhesion and invasion processes. The ompA gene is among the genes responsible for encoding OMPs in bacteria like *Pseudomonas aeruginosa*, and its expression is closely linked to the invasiveness of the bacteria. Deletion of the ompA gene diminishes the adaptability of bacteria to their external environment and disrupts the formation of biofilms [44]. The microbial surface components recognizing adhesive matrix molecules (MSCRAMM) proteins play a crucial role in mediating interactions between bacteria and host cells. This protein family encompasses various adhesive proteins and factors, including clfA, fnbA, fnbB, cna, sdrC, sdrD, sdrE, and spa [45,46]. ClfA, found in *Staphylococcus aureus*, encodes the Clumping factor A protein, which binds to fibrinogen and facilitates bacterial adhesion and invasion in host tissues, thereby promoting biofilm formation and enhancing infection capability. FnbA and fnbB encode Fibronectin-binding proteins A and B, respectively. The interaction of proteins with fibronectin in the host extracellular matrix promotes bacterial adhesion and internalization, facilitating biofilm formation and persistent infection. In *Staphylococcus aureus*, the binding of cna to collagen enables bacterial attachment to host connective tissues and biofilm formation. Additionally, sdr proteins (sdrC, sdrD, sdrE) play a role in mediating interactions between bacteria and host cells or extracellular matrix, thereby promoting biofilm formation and maintenance. Conversely, bacteria residing within biofilms exhibit reduced metabolic activity over an extended period, leading to the development of bacterial mutations into persistent cells or small clones, thereby complicating the eradication of bacteria. In cases of implant-related infections, biofilms are formed by bacteria not only on the prosthesis surface but also at the interfaces of bone and soft tissue in proximity to the prosthesis, posing challenges for complete removal through physical means. Following a course of antibiotic treatment, biofilm infections frequently reoccur despite the surgical removal of the infected implants from the body. Planktonic bacterial cells are liberated from the biofilm, and there is substantiating evidence for the presence of a natural mechanism of programmed detachment. Consequently, if the activated host defenses are unable to eradicate the released planktonic cells at any stage of the infection, the biofilm may act as a focal point for acute infection [47]. The proteins and genes identified play a critical role in the biofilm formation process linked to implant-related infections. Further investigation into these components may enhance comprehension of the mechanisms underlying biofilm formation and antibiotic resistance development, thereby facilitating the development of more efficacious strategies for preventing and treating implant infections.

3. Prevention of biofilm formation - solutions based on morphology, hydrophobicity, and charge changes

When bacteria form a biofilm, the permeability of antibacterial substances is hindered, making sterilization difficult. Hence, the primary strategy for combating biofilm formation involves inhibiting initial adhesion and disrupting the aggregation growth mechanism of bacteria. During the reversible adhesion phase, bacteria primarily utilize hydrogen bonds, electrostatic forces, hydrophobic interactions, and van der Waals forces, along with appendages such as flagella, fimbriae, pili, and extracellular membrane proteins, to detect and adhere to non-biological surfaces or living organism surfaces [48–50]. Several methods have been devised to modify the surface morphology, affinity, hydrophobicity, and charge properties of materials in order to prevent non-specific adsorption of bacteria [51–53]. The surface morphology of materials is typically characterized by roughness (disordered) and morphological pattern (ordered and repeating three-dimensional structure array), both of which have been shown in numerous studies to significantly influence bacterial adhesion and biofilm formation [54,55]. The adhesion of bacteria is influenced by changes in the surface energy and hydrophobicity of materials as the contact area varies. An increase in roughness does not always result in a corresponding increase in cell adhesion and film formation, with a critical threshold of roughness often associated with the highest bacterial adhesion capability. The anti-adhesion properties of materials are also dependent on the specific type of bacteria present, as evidenced by varying adhesion behaviors exhibited by bacilli and cocci on the same surface [56]. The relationship between topographic pattern size and bacterial cell size is a crucial factor in determining bacterial adhesion behavior [57]. Lu *et. al.* demonstrated that adhesion can be substantially decreased when the distance between three-dimensional structures is less than the size of the bacteria [58]. Consequently, altering the roughness of material surfaces presents a significant challenge due to the uncertainty surrounding this phenomenon. Researchers are investigating morphological patterns that have the potential to impact cell adhesion and bactericidal activity through direct contact, with a notable example being the tip-like matrix pattern. In a study by Hayles *et. al.*, an antimicrobial surface was developed for use in preventive surgery, featuring sharp nano spikes that increased the susceptibility of *Staphylococcus aureus* to antibiotics. The researchers observed that upon adherence to a titanium surface, *S. aureus* altered its cell surface charge, leading to heightened resistance to vancomycin. Moreover, when the titanium surface is enhanced with nano spikes, it results in the revitalization of vancomycin activity, ultimately promoting enhanced bacterial cell death through synergistic mechanisms [59]. Additionally, a surface modification technique involving tip-polishing, resembling the structure of a cicada wing [60], has been shown to effectively penetrate the cell wall of Gram-negative bacteria attached to the surface, consequently leading to bacterial eradication [61]. The composition of the bacteria's cell wall primarily consists of carbohydrates and amino acids, with the teichoic acid within the cell wall containing numerous highly acidic phosphate groups. When the pH of the human body fluid environment exceeds the bacteria's isoelectric point, the bacteria acquire a negative charge. Leveraging the principles of charge attraction and repulsion, researchers have devised a range of zwitterionic materials that impede the attachment of bacteria and their proteins. Zwitterionic polymers exhibit two primary attributes: (1) Charge neutrality, wherein positive and negative charge groups are present in equal proportions, and (2) Dipole minimization, achieved through the even distribution of positive and negative charges at the molecular level. These inherent characteristics render zwitterionic polymers resistant to the electrostatic adsorption of proteins, as charges are locally generated [62]. A notable example of natural zwitterions are amino acids, characterized by the direct linkage of carboxyl (-COOH) and amino (-NH2) groups to the central alpha carbon atom. Liu *et. al.* successfully synthesized a coating surface utilizing natural amino acid zwitterionic polymers (pAAZ). Their findings demonstrated that the pAAZ coating effectively prevented the adsorption of undiluted human serum and plasma, as well as significantly hindered the long-term bacterial adhesion of epidermal Gram-positive *Staphylococcus aureus* and Gram-negative *Pseudomonas aeruginosa* [63]. Additionally, various methods for integrating materials with distinct charge components to create zwitterionic polymer surfaces have been established in the literature [64–69]. Amphoteric materials exhibit versatility in their applications, serving not only as coatings to directly combat bacteria, but also as vehicles for antibiotics to enhance their penetration and delivery into biofilms, ultimately leading to improved bactericidal efficacy [70,71].

4. Destroy the biofilm structure - a sustained antibacterial strategy based on the synergy of antibacterial substances, physics, and chemistry

Once a biofilm has formed, its intricate structure and alterations in bacterial metabolism render traditional antibiotic treatments ineffective in completely eradicating the pathogen. Therefore, it is imperative to outline key strategies for the complete removal of biofilm: Step 1 involves disintegrating the biofilm, converting adherent bacteria into

planktonic bacteria, and establishing entry channels for the penetration of antibacterial substances. Step 2 entails prolonged, high-concentration sterilization. Step 3 emphasizes the importance of preventing the emergence of drug-resistant bacteria. Researchers utilize physical and chemical methods, such as exogenous heat or the generation of endogenous reactive oxygen species (ROS), to expedite the disintegration of biofilms by loosening and decomposing their structure. Emerging antibiofilm nanomedicine treatment technologies, including photothermal therapy (PTT) [72,73], photodynamic therapy (PDT) [74–76], immunotherapy [77], chemodynamic therapy (CDT) [78] and sonodynamic therapy (SDT) [79–81] demonstrate promising prospects for broad application. For instance, many contemporary treatment strategies incorporate synergistic combinations of various therapies in order to optimize the sterilization efficacy through mutual reinforcement [82]. One such approach is the utilization of combined photothermal therapy, wherein the photothermal stimulation of bacterial membrane permeability facilitates the intracellular delivery of antibacterial agents. This method also amplifies the production of reactive oxygen species (ROS) by photosensitizers/sonosensitizers and facilitates the recruitment of immune cells. This integrated therapeutic approach addresses the deficiencies present in existing single treatment models, such as inadequate sterilization, cytotoxicity, limited drug permeability, and adverse immune responses.

Antibiotics play a crucial role in the prevention and treatment of orthopedic implant infections and are commonly utilized in antibacterial coatings. The protective barrier created by biofilm poses a challenge for traditional antibiotics to achieve complete eradication of bacteria. Failure to completely eliminate bacteria can lead to the development of drug-resistant mutations due to prolonged exposure to low concentrations of antibiotics. The utilization of coating-sustained-release, pH-responsive, targeting, and other strategies effectively addresses the challenge of rapid early release of antibiotics, facilitating precise, sustained, and controllable drug delivery. These innovative approaches offer novel solutions to this issue [83]. However, the combination of antibiotic therapy with photothermal therapy and hemodynamic therapy significantly enhances efficacy, yet potential risks of cytotoxicity and drug resistance persist. Hence, researchers have been diligently seeking alternative non-antibiotic-dependent strategies, such as inhibiting bacterial metabolism, disrupting extracellular polymer EPS production, or interfering with quorum sensing, in order to identify safer and more environmentally friendly targets. Contemporary molecular methodologies have demonstrated that conventional non-antibiotic agents like copper ions, silver ions, iron ions, selenium, sulfur [84], ethylenediaminetetraacetic acid, among others, can impede bacterial energy metabolism and efflux pump function without eliciting concerns regarding drug resistance. The preservation of the envelope's structural integrity is essential for the sustenance of bacterial viability, virulence, and physiological function. Within eukaryotic cells, the production of reactive oxygen species, facilitated by unstable iron free radicals in the Fenton chemistry reaction, induces lipid peroxidation of the cell membrane's lipid bilayer, leading to cellular damage and initiation of ferroptosis [85]. While ferroptosis has traditionally been observed in eukaryotic organisms, recent studies suggest its potential presence in prokaryotes, presenting a novel therapeutic avenue for combating pathogenic infections [86,87]. For instance, Hu *et. al.* developed a treatment system utilizing cinnamaldehyde-ferric oxide in conjunction with sonodynamic therapy, which resulted in a notable reduction of bacterial load in the lungs of mice infected with MRSA. This treatment also mitigated inflammatory damage without causing apparent cytotoxic effects [88]. Additionally, approaches aimed at disrupting bacterial energy metabolism, disrupting homeostasis, and compromising cell membranes, such as cuproptosis, exhibit distinctive features such as extensive reactive oxygen species generation, superoxide accumulation, glutathione depletion, and respiratory chain inhibition [89]. Furthermore, antibacterial solutions utilizing cuproptosis and ferroptosis have demonstrated the ability to inhibit bacterial quorum sensing systems, eradicate biofilms, and diminish virulence. These alternative sterilization techniques, which do not rely on antibiotics, offer promising avenues for addressing microbial resistance and combating infections associated with biofilms. They also present potential targets and a theoretical framework for the clinical management of orthopedic infections related to biofilms.

5. Immune reactivation and reconstruction

The intricate etiology of immunosuppression induced by endophytes and biofilms has long impeded the effective treatment of endophyte infections. In the presence of endophytes, the local immune milieu is disrupted, while biofilms hinder the activity of peripheral immune cells, particularly antigen-presenting cells (APCs), leading to inadequate antigen presentation and ultimately insufficient immune activation in the host [90–92]. In contrast to planktonic bacteria, the immunogenicity of bacteria-associated antigens within biofilms is significantly reduced, leading to inadequate antigen recognition and heightened depletion of antigen-presenting cells, T cell suppression, and compromised B cell activation, ultimately resulting in a biofilm-specific immune deficiency [90,93]. Bacteria within biofilms have been shown to indirectly induce immune cell dysfunction by producing elevated levels of peroxides, metabolic toxins, and acidic byproducts, leading to phenomena such as heightened M2 polarization of macrophages and impaired function of dendritic cells, as well as an increase in regulatory Tregs. This cascade of events results in heightened expression of immunosuppressive cytokines and immune checkpoint molecules, decreased infiltration of effector T cells, and ultimately exacerbates local immune suppression [94–96]. Conversely, pathogenic bacteria have the ability to disrupt host cell autophagy activity by means of outer membrane vesicles, thereby impeding the activation of inflammatory signaling pathways and resulting in compromised host immune function [97,98]. Recent research has demonstrated that bacteria have the capability to generate a harmful biofilm on immune cell surfaces, leading to their destruction [99]. Consequently, there is a pressing necessity for the exploration and implementation of novel therapeutic approaches aimed at altering the immune milieu in order to suppress biofilm formation. Of particular interest is the potential of cuproptosis and ferroptosis, processes that disrupt bacterial energy metabolism, to not only activate local immune responses but also reconfigure the immune microenvironment at the site of infection. This could result in sustained antibacterial effects across all stages of infection and prevent potential recurrences. Iron ions play a crucial role in various biological processes, including DNA synthesis, respiration, toxicity, and biofilm formation. Bacterial biofilms have the ability to sequester iron ions, thereby impeding the exchange of ions and self-regulatory activities related to iron metabolism in surrounding innate immune cells, such as neutrophils. Consequently, antibacterial approaches that induce iron overload in bacteria and facilitate the restoration of iron-trophic neutrophils have demonstrated efficacy [89,100]. Moreover, the utilization of a cuproptosis-based approach involving copper polyoxymetalate clusters (Cu-POM) in conjunction with gentle photothermal therapy and activation of macrophage immunity effectively eliminated biofilms at all developmental stages. The overabundance of intracellular copper ions hinders the bacterial tricarboxylic acid cycle, impeding energy utilization, fostering peroxide buildup in bacteria, disrupting lipid membranes, and facilitating the restoration of impaired macrophage functions, thereby hastening the secretion of chemotaxis, phagocytosis, and pro-inflammatory cytokines, ultimately ensnaring planktonic bacteria attempting to evade the deteriorating biofilm [101]. In contrast to cuproptosis and ferroptosis in the context of immune remodeling, reactive oxygen species (ROS) serves as a pivotal factor in the immune remodeling process by initiating the reactivation of macrophage function. Upon phagocytosis of bacteria, macrophages produce an ample amount of ROS within their cells to effectively eliminate the internalized bacteria. As a result of persistent bacterial invasion, macrophages transition from the bactericidal M1

phenotype to the anti-inflammatory M2 phenotype, leading to inadequate reactive oxygen species (ROS) production. Targeting macrophages in vivo with ROS-releasing particles can enhance their bactericidal capabilities by facilitating responsive release of ROS at the site of infection, promoting macrophage-specific uptake and in vitro manipulation to induce sufficient ROS production for intracellular bacterial elimination and M1 repolarization [102]. The relationship between immune function and biofilm formation is significant. Strategies for bacterial immune remodeling can effectively interfere with bacterial metabolism and activate local adaptive immunity, offering a comprehensive approach to treating refractory biofilm-related infections and biofilm-induced local immune suppression.

6. Summary and outlook

The management of endophytic biofilm-associated infections represents a significant focus of clinical investigation within the field of orthopedics. This paper provides an overview of the three primary material-based treatment approaches that correspond to distinct stages of the biofilm formation process. It elucidates the potential utility of diverse physical and chemical interventions in the prevention and management of implant-related infections, as evidenced by recent research findings. The management of biofilm formation necessitates a comprehensive, prolonged, consistent, and adjustable multi-modal treatment strategy. The development of composite materials should be informed by the biological properties of endophytic infections and aim to achieve a synergistic bactericidal outcome. The investigation into novel mechanisms for disrupting biofilms suggests that the integration of advanced biological and material technologies may represent a promising avenue for addressing biofilm-related infections in the future. The development of innovative antibacterial agents, novel drug delivery approaches, identification of therapeutic targets, and exploration of combination therapies hold potential for overcoming this formidable challenge.

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Consent for publication

All authors concur with the submission and publication of this paper.

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Zhuoer Pan: Writing – original draft. **Chengxin Dai:** Writing – review & editing. **Weixu Li:** Writing – review & editing.

Declaration of competing interest

All co-authors have read and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and the content is not submitted to or under review by any other journals.

Data availability

Data will be made available on request.

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