REVIEW

# Bacterial biofilms: Basic characteristics and strategies for the treatment of bacterial wound infections

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## ABSTRACT

Bacterial biofilms (BFs) are widely present in nature, and more than 99% of bacteria can form BF, which is an important factor leading to persistent infection of refractory wound and repeated infection. The formation of BF is a dynamic cyclic process involving various physical, chemical and biological processes, mainly including bacterial attachment, BF formation and maturation, and bacterial diffusion. The bacteria in bacterial biofilms are more resistant to antibiotics and disinfectants, and more resilient to environmental changes, which presents many challenges in treatment. This article reviews the basic characteristics, resistance mechanisms and treatment strategies of BF. At present, there are many studies on the treatment of BF, which need to be selected according to the specific situation and pathophysiological process of wound infection, and can be used as a single method or in combination. This article introduces some treatment methods to provide a reference for the clinical prevention and treatment of BF.

**Key Words:** Bacterial biofilms, Characteristics, Wounds, Infection, Treatment

## 1. INTRODUCTION

Bacterial biofilms (BFs) are widely present in nature, and BF is paid more and more attention by the public. BF is a highly heterogeneous and dynamically changing, and BF shows complex responses to different environmental factors.[1] More than 99% of bacteria in nature can form BF, and the bacteria in BF can be in the dormant status with still growth and no more division, and regrow when conditions are appropriate, resulting in persistent and repeated infection.[2] It has been reported in the literature that BF is associated with at least 80% of bacterial infections in humans,[3] and the detection rate of BF in chronic wounds is 78.2%,[4] in comparison with only 6% in acute wounds,[5] the infection caused by BF in chronic wounds needs high clinical attention. There are 100 million patients receiving the treatment of wound infection in China every year, of which 30 million are classified into difficult wound infection treatment.[6] For different types of infectious wounds, early diagnosis and targeted treatment measures are required. Chronic wound is a large category of diseases with complex etiology, the core and difficulty of clinical diagnosis and treatment lies in accurate diagnosis and differential diagnosis.[7] In chronic wounds, bacteria mostly exist in the form of BF, and the bacterial resistance is enhanced, and

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it is difficult to be removed, and continuous stimulation of wounds can produce inflammatory response, and the wound is more difficult to heal. Drug-resistant bacteria with strong BF formation ability are important factors in chronic and persistent infections in hospital environments.[8] The treatment of chronic wounds includes the application of new dressings, anti-BF therapy, negative pressure occlusion and drainage, hyperbaric oxygen therapy, growth factor therapy, stem cell therapy, etc., among which the treatment measures for BF play an important role.[9]

## 2. The formation process and basic characteristics of BF

### 2.1 The basic form of BF

Most microorganisms exist in a community in the form of a spatial structure in micron units.[1] BF is a three-dimensional microbial community with extracellular polymers containing polysaccharides, lipids, proteins, extracellular DNA (eDNA), bacterial outer membrane vesicles (OMV), Ca2+, etc. as the main components, encapsulated and attached to the surface of living or abiotic organisms.[10–12] In well-developed BFs, EPS accounts for 90% of the biofilm volume and bacteria account for only 10%.[13] The bacteria within the BF are more resistant to antibiotics and disinfectants and more resilient to environmental changes.[14]

### 2.2 The formation process of BF

The formation of BF is a dynamic cyclic process involving various physical, chemical and biological processes, mainly including bacterial attachment, BF formation and maturation, and bacterial diffusion.[15] The classical BF formation process includes five stages, the first stage is the adhesion of bacteria to the surface of objects through fimli and flagella, which is called reversible attachment; In the second stage, the reversal rate of bacterial flagellar decreases, with gene expression decreasing and EPS formed, and the bacteria produce drug tolerance, which is called irreversible attachment; In the third stage, multiple bacterial clusters appear in the BF, which is called maturation stage I., and the formation of fully mature microcolonies in the fourth stage is called maturation stage II. In the fifth stage, the various enzymes formed by the BF can degrade the EPS, causing the bacteria within the BF to be released, called dispersion, to re-enter the next progressive cycle, and lead to the spread of infection.[16] Sauer K proposed a three-step model for the expansion of BF formation, the first step is aggregation and adhesion, where bacteria aggregate or adhere to their surfaces; in the second step is expansion for bacterial growth and accumulation; The third step is depolymerization and separation, in which the bacteria are detached from the BF in aggregate or monomer form. Compared with the traditional 5 stages, the 3-step model includes the BF formation process under all different conditions and microenvironments, and the model is relatively simple and generalized, which is conducive to the understanding and research of BF.[16]

### 2.3 The basic characteristics of BF

Literature studies indicated that BF as a whole expanded vertically from the matrix, some bacteria expanded outwards in a catapulting manner, while others were trapped on the matrix. In general, a collective fountain-like flow was formed, and some bacteria were transported to the front of BF, making BF rapidly expand laterally, suggesting that the fountain-like flow of bacteria promoted the expansion of BF.[17] Bacterial adhesion fimbrii play an important role. Bacterial fimbrii can secrete proteins that promote the formation of BF. Fimbriin is a kind of protein-like extracellular fiber, which plays an important role in the development of BF on both biological and abiotic surfaces of bacteria.[18,19] The extracellular matrix of BF contains a large amount of proteins, including fimbrii, type IV fimbrii and a variety of enzymes secreted by bacteria (such as proteases). Type IV fimbrii can also bind to other components in BF to make BF more stable.[20] Some passive physical phenomena observed in the extracellular matrix of BF, such as liquid-liquid phase separation, glass transition, and transmembrane transport of metal ions, jointly affect the morphology, structure, and ability of BF to cope with environmental stress, revealing how bacteria use these passive physical mechanisms to enhance the function of BF.[21] The polysaccharide matrix in EPS usually refers to polysaccharide protein complexes, as well as organic and inorganic substances precipitated by the periphery,[22] which maintain the skeleton structure of BF, prevent the penetration of antibiotics by physical or chemical means, inhibit the chemotaxis and antimicrobial peptide activity of neutrophils, and scavenge reactive oxygen species, which contribute to the survival of bacteria.[23] The outer membrane of BF also acts as a physical and mechanical barrier to maintain basic cellular physiology.[19] eDNA is DNA that is actively released, secreted by bacteria, or released in the extracellular matrix after bacterial dissolution, and plays a very important role in bacterial activities. When environmental pressure conditions such as temperature, nutritional deficiency, and antibiotics change, bacteria in BF will increase the production of OMV, which will promote BF formation and survival.[24] A study of photosynthetic bacteria biofilms found that there were a large number of small water channels inside the three-dimensional structure formed by BF. The water channels diffused the nutrients transmitted by the light source to the bacteria inside the BF for absorption and utilization, and the metabolic products of the bacteria were diffused to the

outside through these water channels.[25]

### 2.4 The "hijacking" theory of bacteria and persisters

Mirzaei R proposed the "hijacking" theory of bacteria, in which DNA, hyaluronic acid, collagen, fibronectin, f-actin, and plasma can be incorporated into EPS through different mechanisms and play an important role in different stages of BF formation in chronic infections caused by BF.[26] Arciola CR states that metabolically inactive bacteria with very low growth rates and cell division rates exist deeply in BF, called persister cells or persisters, are reactivated as new BF hosts when conditions permit, leading to recurrence of bacterial infections or the formation of chronic infections.[27] It was found that non-attached BF aggregates exhibited higher antimicrobial resistance and immune evasion ability than planktonic bacteria,[28] temperature affects BF yield, density, structure and morphology. At 20°C, the total biomass and thickness of Pseudomonas aeruginosa are increased significantly, and the structure, gene and protein expression of BF are changed.[29,30]

## 3. The main mechanisms of resistance in BF

There are many factors that lead to the development of antibiotic resistance to BF, which is a dynamic and multi-factored process, and BF requires higher concentrations and longer antibiotic treatment than free bacteria.[31] The resistance of bacteria in BF to antibiotics was 10-1000 times higher than that of planktonic bacteria, it was mainly because the MBC value of antibiotics was reduced, while there was no significant difference in MIC value. When bacteria left BF, their drug sensitivity was the same as that of plankton bacteria.[32]

### 3.1 The barrier effect of BF

The interaction of antibiotics with EPS causes its spread to slow down, and bacteria have more time to initiate an adaptive stress response, increasing the resistance to antibiotics.[33] The permeability of vancomycin, oxacillin, cefotaxime, and delafloxacin in staphylococcal biofilm matrix is different, while the permeability of ciprofloxacin and amikacin is less affected by EPS.[34] The activity of antibiotics is affected by the growth rate and physiological state of bacteria. $\beta$-lactam drugs and tetracycline drugs act on the cell walls and ribosomes respectively, and have poor effects on slow-growing bacteria, while gentamicin, ciprofloxacin and rifamipine show better effects on non-growing bacteria.[35] Through the study of Acinetobacter Baumannii AB5075, it is proved that the bacterial polysaccharide part can mediate the resistance to antibiotics at the single-cell level, and the structure of BF protects the bacteria at the community level.[36]

### 3.2 The role of the quorum sensing system

Bacteria have the ability to adapt to new environments and sense environmental changes, Quorum sensing system (Quorum sensing, QS) is the bacterial signal communication system, which can generate and release signal substances by quorum sensing in the BF formation process to regulate the synthesis and secretion of various signal molecules, thereby interfering with bacterial adhesion and colonization, BF maturation and dispersion, affecting the spread of bacterial resistance.[37] After the bacterial density reaches a certain threshold, QS undergoes cell density-dependent gene expression regulation, which affects the expression of different genes in bacteria, including BF formation, bacterial drug resistance and virulence factors.[38] QS is a cell-to-cell communication mechanism, which detects the changes in population density through the accumulation of signaling molecules produced by bacteria themselves, regulates the expression of related genes, promotes the formation and dispersion of BF, ensures the transportation of nutrients required for the normal growth of BF and the discharge of produced wastes, and avoids the lack of living space and nutrients caused by bacterial overgrowth.[39]

### 3.3 The immune evasion of BF

The barrier effect of BF hinders the immune effect of specific antibodies, sensitizing T cells, natural killer cells, phagocytic cells and lysozyme on bacteria, reduces or inhibits the strength of the body's immune response by reducing the production of cytokines or enzymatic hydrolysis of cytokines, produces mucopolysaccharides to inhibit the phagocytosis of monocytic macrophages and reduce their chemotaxis activity, neutralizes the activity of oxygen mediators, and stimulates the body to produce more antibodies to form immune complexes.[40] It was reported that Staphylococcus aureus incorporated fibrin into EPS through the expression of coagulase to protect BF from recognition by the immune system.[41]

### 3.4 The role of resistance genes in BF

It has been reported that OMV can carry plasmid DNA, chromosome DNA, phage DNA or RNA, etc., and prevent the degradation, freezing inactivation and thermal degradation of exonuclease, and transfer the plasmids of antibiotic resistance genes (ARG) between bacteria, which promotes horizontal gene transfer (HGT).[42] ARG in BF can be horizontally transferred through transformation, transduction and binding, and bacteria in biofilms can enhance the expression of efflux pumps to pump intracellular toxins (including antibiotic drugs) out of cells.[43] It is reported in the study that complex metabolite exchange processes between cells in different regions of BF can enhance BF resistance through material exchange by reducing the energy demand of external

cells and helping internal cell repair.[44]

### 3.5 Persisters

Persisters can escape from the attack of host immune system and kill antibacterial drugs, which is an important cause of the recurrence of infection and chronic infection.[45] In particular, antibiotic-resistant persisters continue to reproduce and disperse from BF to form new BF, which is an important reason for the persistence of infection.[46] Clinically, after the interruption of antibiotic treatment, the dormant persisters are reactivated, resulting in the repeated formation of BF.

## 4. Treatment strategies for wound BF infection

Wound BF infection is complicated and varied. There are many treatment methods for BF, and it is necessary to choose according to the specific situation of wound infection and the pathophysiological process. A single method can be used or multiple methods can be used in combination. In clinical work, attention should be paid to the infection caused by multi-species co-existence. Literatures indicate that in a stable multi-species co-existing bacterial community, many co-existing bacterial species cannot coexist in paired culture under the same conditions, showing strong competition and exclusion, while they can coexist in a multi-species community, suggesting that multi-species co-existence is an emergent phenomenon.[47] In addition, there is a microbiota on the normal skin of the human body, the human body is a super organism composed of human cells and microorganisms, and no longer just made up of our own cells, but a complex ecosystem.

### 4.1 Strengthen wound management, remove BF, and control wound infection

The wound treatment should be done in accordance with the principle of standard wound treatment, among which debridement is the most effective way to remove or reduce BF. International Wound Infection Institution recommends sustained-release iodine as a first-line therapy to remove wound bacteria (including plankton and biofilm bacteria).[48] In vitro tests indicate that the povidone iodine solution, silver-containing dressings, honey, surfactants and other topical preparations all show certain BF removal effects. Among them, the povidone iodine solution is the most effective way to reduce bacterial content, which can penetrate and destroy BF.[49] The novel wound dressing anti-biofilm protein asymmetric release system has a significant effect in inhibiting or dispersing BF, with a clearance rate of up to 80%.[50]

### 4.2 The regulation of BF-formation related proteins and genes and the anti-infection effect

The BF-formation related proteins (Bap proteins) may become a potential therapeutic target, thereby inhibiting the formation of BFref:19. Bacterial binding to abiotic sites is achieved through pilates (Cus pilates) and outer membrane protein A (OMPA), and inhibiting this binding site can hinder BF formation. Phelpinol, a polyphenol organic compound extracted from several tree barks, can reduce the motility of BF and downregulate genes related to cell adhesion (OmpA, CSUA/B), inhibiting the formation of BF.[51] A bicyclic monoterpene alcohol (myrtenol) found in a variety of plants can cause a significant decrease in BF thickness and surface coverage, as well as a decrease in hydrophobicity, motility, and the expression of BF-related genes such as bfmR, CUSA/B, bap, ompA, pgaA, and pgaC.[52]

### 4.3 Related therapeutic measures to inhibit QS signal transmission

Bacteria achieve the transmission between intra- and inter-bacterial groups through QS mechanism. The QS inhibitor is a new generation of antibacterial agents, mainly N-acetylhomoserine lactone (AHL) antagonists that bind LuxR type receptors. They inhibit natural AHL binding by competing for binding sites, so that LuxR homologs will not be activated and virulence factors will not be expressed. In addition, there are AHL synthesis inhibitors to hinder AHL synthesis.[53] It has been reported that linalool, an oil compound extracted from coriander, inhibits the biofilm formation of Acinetobacter baumannii by affecting bacterial adhesion and interfering QS.[54]

### 4.4 The destruction of EPS improves the bactericidal effect of antibiotics

Small molecule inhibition of extracellular polysaccharide modification enzymes can block the formation of extracellular polysaccharide Pel-dependent BF, which can target small molecule inhibitors to block the development of Pel-dependent BF in Gram-positive and Gram-negative bacteria.[55] Proteolytic enzymes can degrade matrix proteins and adhesions in EPS. Literatures have reported that the antibiotic nanogel carrier that encapsulates protease Alcalase can destroy EPS through protease, so that antibiotics can work. It is effective against Staphylococcus aureus, Pseudomonas aeruginosa, Staphylococcus epidermis, Klebsiella pneumoniae, E. coli and Enterococcus faecalis in the formation of wound BF. Compared with ciprofloxacin alone, nanogels wrapped with ciprofloxacin and alkaline protease can reduce Staphylococcus aureus in BF.[56] Deoxyribonuclease 1 (DNase I) degrades the eDNA of the longest molecule in EPS by hydrolyzing the phosphodiester bonds of the phos-

phate backbone, and degrades the biofilms of Staphylococcus aureus and Pseudomonas aeruginosa.[57]

### 4.5 Inhibit the efflux pump effect of bacteria and enhance the effect of drugs on BF

There is a large class of protein pumps in the bacterial membrane, which can excrete antibiotics out of the cell, efflux pump inhibitors (Epis) can block antibiotic efflux, and thioxanthones have antibacterial activity and inhibition effects of efflux pumps, BF formation and QS.[58] Phenylarginine $\beta$-naphthylamine (PARN), carbonyl cyano-chlorophenzide (CCCP), INF271, INF55 have inhibitory effects on bacterial effluents.[59]

### 4.6 Anti-BF antibody is used to exert anti-BF effect

MFb, a monoclonal antibody against alginate scFv-Fc, could reduce the adhesion and invasion of Pseudomonas aeruginosa on HeLa cells, and inhibit the formation of biofilms of Pseudomonas aeruginosa. MFb enhances the phagocytosis of macrophages in a concentration-dependent manner, with a protective effect on HeLa cells.[60] Human monoclonal antibody (TRL1068) has been reported in the literature to show anti-BF efficacy in vitro; The antibody is verified to promote the dispersed clearance of BF by catheter-associated rat infection model testing, suggesting that TRL1068 can be used for clinical treatment.[61]

### 4.7 Interfere with iron metabolic pathways, bacterial reproduction and BF formation

Iron is an essential nutrient for almost all living things, and bacteria are able to use extracellular iron through siderophores to promote their growth as well as the maturation of BF.[62] Iron uptake is contested using iron antagonists or iron chelators, which can chelate iron in an environment where bacteria grow, interfering with bacterial reproduction and BF formation.[63] Lactroferrin is a natural chelating agent. Literatures have reported that lactoferrin ALX-009 can reduce the biofilm formation of Pseudomonas aeruginosa, enhance tobramycin and azutranan to inhibit Pseudomonas aeruginosa biofilm formation and enhance the ability to remove BF that have been formed.[64]

### 4.8 Antimicrobial peptides (AMP) for BF infection

AMPs are a type of cationic peptide compounds that are widely present in plants and animals and can exhibit broad-spectrum antibacterial activity through a variety of pathways. AMPs mainly show activity by inducing the formation of bacterial transmembrane pores and membrane cleavage. In addition, they can flocculate bacterial contents and bind to nucleic acids, inhibit the synthesis of bacterial cell walls, proteins and nucleic acid.[65] AMPs have broad-spectrum anti-BF activity and the ability to favorably modulate host immune responses;[66] It can penetrate BF, inhibit the formation of BF, have strong antibacterial activity, enhance the activity of antibiotics against BF, and show synergy with vancomycin, penicillin, $\beta$-lactam antibacterial drugs, azithromycin, linezolid, etc., and at the same time mediate inflammatory responses, promote cytokine release, cell proliferation, angiogenesis and wound healing.[67] Literatures have reported that polyproline peptide AMP bac (1-35) can destroy BF formed by Klebsiella pneumoniae, expose bacteria and exert efficient antibacterial activity.[68]

### 4.9 Anti-BF effects of nanoparticles and nanomaterials

Nanomaterials are divided into metal-based nanomaterials, inorganic non-metallic nanomaterials and organic nanomaterials. Nanomaterials have unique physical and chemical properties and strong bactericidal activity, which inhibit the growth of BF through physical damage, oxidative stress, thermal damage, etc., and the application of nanoparticles on the surface of implant materials can prevent BF formation.[69] Metal-based nanomaterials such as magnetic iron oxide nanoparticles, silver nanoparticles and gold nanoparticles show good anti-BF activity, and a variety of organic nanoparticles also show significant anti-BF activity and good biocompatibility.[70] Lipid nanopreparations, polymer nanoparticles (such as chitosan, alginic acid, cellulose and hyaluronic acid), microneedles and magnetite have good biocompatibility and are widely used as carriers for the delivery of antimicrobial drugs in chronic wound BF infection.[71] AgNPs can inhibit BF formation of Acinetobacter baumannii, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli and Klebsiella pneumoniae by inhibiting the expression of different virulence-related genes kpsMII, afa/draBC and BF-related genes (bap, OmpA and csuA/B).[72] The carbon-based material of bifunctional preparation is a new type of nanomaterial. For example, graphene, fullerene, carbon nanotubes, carbon nanofibers and their derivatives can be combined with other nanomaterials to form composite nanomaterials for the treatment of chronic wounds. The nanocomplex prepared by multi-wall carbon nanotubes and hydroxyapatite, zinc oxide and silver nanoparticles have significant antibacterial activity.[73]

### 4.10 Bacteriophages for BF infection

Bacteriophages are one of the most abundant viruses on earth, and they only infect bacteria instead of eukaryotic cells. Bacteriophage therapy is gaining more and more attention, especially for superdrug-resistant bacterial infections.[74] The application methods of phage include monophage dilution, multiphage cocktails, phage-derived proteins, mixtures of phages and different antibiotics, and transgenic phages. The

literatures have reported that cocktails of six phages can eliminate 95% of BF within 4 hours.[75] The phages VB Saum-A, VB Saum-C and VB Saum-D are effective anti-BF agents.[76] Treatment with phages can reduce BF survival rate and metabolic activity of Pseudomonas aeruginosa strains in the endotracheal tube-related BF model,[77] and the combination with ciprofloxacin is effective in clearing Pseudomonas aeruginosa biofilms.[78] "Engineered phages" are designed to cleave biofilms using genetic engineering that can enable ordinary phages to express depolymerases, thereby obtaining the ability to cleave biofilms. Genetic engineering technology is used to expand the phage host range and the survival rate in EPS to increase the degradation of BF.[79] The synthetic phage genomics CRISPR-Cas system has been reported in the literature for the fabrication of a large number of phages, and it is now possible to construct a genome > 500 kb for on-demand phage production.[80] The clinical application of phage therapy still faces some risks and challenges, such as the use of a single type of phages with a narrow host spectrum, the release of endotoxins to trigger an inflammatory response, and the reduced effect of phage neutralizing antibodies.[81] Phage predation increases the spread of plasmid-encoded antibiotic resistance in microbial ecosystems.[82] The development of precise phage mixtures guided by genomic monitoring has been reported in the literature, providing a framework for precise phage therapy in the clinic.[83]

### 4.11 The role of natural medicines and Chinese patent medicines in anti-BF

There are many researches on Chinese patent medicine and natural medicine extracts, which have remarkable effect on anti-BF. Baicalin can reduce the adhesion of Staphylococcus aureus, inhibit and clear its BF, and is used in combination with ceftazidime, cefazolin, levofloxacin, vancomycin, etc., which can accelerate the destruction of the structure of BF, enhance the penetration of antibiotics and the removal of bacteria.[84] A certain concentration of berberine hydrochloride, baicalin and quercetin dihydrate can inhibit the formation of Acinetobacter baumannii biofilm and the adhesion ability to medical materials, and the combination with meropenem, imipenem and tigecycline can improve the inhibition rate of Acinetobacter baumannii biofilm.[85] Zerumbone extracted from Zingiber zerumbet can reduce the formation of Acinetobacter baumannii biofilm and destroy BF that has been formed.[86] Cannabigerol has inhibitory and bactericidal activity against Streptococcus mutans biofilms.[87] AMP extracted from red pepper has antibacterial adhesion properties and can prevent the formation of Staphylococcus epidermidis biofilms.[88] Plant-derived carvacrol restores the sensitivity of methicillin-resistant Staphylococcus aureus biofilms to $\beta$-lactams.[89] Terpenoids and phenolic compounds in plant essential oil (EO), litsea cubeba essential oil, tea tree essential oil, clove essential oil, oregano essential oil, thyme essential oil, cinnamon essential oil, etc., have anti-BF activity against methicillin-resistant Staphylococcus aureus, Escherichia coli, drug-resistant Acinetobacter baumannii, etc.[90,91]

### 4.12 Application of probiotics and their derivatives

Probiotics can inhibit the growth, adhesion and aggregation of pathogens, regulate the microbial ecology of BF, and exert antibacterial activity against pathogens in the gastrointestinal tract by lowering pH, competing for adhesion sites and nutrients, and producing bacteriocins, hydrogen peroxide and organic acids.[92] The next generation of probiotic NGP is a new type of probiotic strain optimized or modified by modern scientific and technological means (such as genetic engineering, molecular biology, etc.), and has good application and potential.[93]

### 4.13 Anti-BF effect of Antimicrobial photodynamic therapy (aPDT)

Phototherapy refers to light-mediated techniques, that is, those that use visible and/or invisible light to treat in a minimally invasive way, mainly including photodynamic therapy, ultraviolet irradiation, blue light, low-level laser therapy, etc. Photodynamic therapy uses a specific wavelength of light to activate photosensitizers and produce reactive oxygen species in the presence of aerobic oxygen to achieve an antimicrobial effect, and studies have shown that this therapy can destroy the biofilm of pathogens. The photosensitizer enters BF and binds to EPS and bacteria, which promotes the excitation of aPDT to produce a large number of reactive oxygen species (ROS), which oxidizes the polysaccharides of EPS, lipids on the surface of bacteria, and proteins and DNA in bacteria, resulting in EPS destruction and bacterial disintegration.[94] aPDT has antibacterial and anti-BF effects, PDT (810 nm, 1 min) can down-regulate the expression levels of QS genes abaI, agrA and Iasi of Acinetobacter baumannii, Pseudomonas aeruginosa and Staphylococcus aureus photosensitized by indocyanine green (ICG, 31.2 $\mu$g/mL), inhibit the transmission of QS signals, and has the characteristics of antibacteria, anti-BF, gene expression inhibition and ROS production, which can be used for the treatment of burn wound infection.[95] The combination of methylene blue and gentamicin with aPDT has a significant photoinactivation effect on the biofilms of Staphylococcus aureus and Pseudomonas aeruginosa.[96] The combination of aPDT and antibiotics can treat the related infections caused by biofilm of multidrug-resistant bacteria, and antimicrobial blue light (aBL) has a significant antibacterial effect on multidrug-resistant bacteria and BF, and has a synergis-

tic effect with antibiotics.[97] Photocatalytic UVC irradiation with TiO2 effectively reduce EPS in BF constructed by two-species mixture (TSM) of Pseudomonas aeruginosa and Staphylococcus aureus, inhibit the secretion of its interspecific quorum-sensing signaling molecule autoinducer-2 (AI-2), down-regulate the expression of related genes, thereby completely killing TSM biofilms.[98]

### 4.14 The therapeutic role of ultrasound in BF infection

Ultrasonic microbubble technology can destroy BF, increase the permeability of BF through the sound hole effect of ultrasound, and further exert the role of antibiotics. Ultrasonic microbubbles can be modified by certain antibiotics. The modified microbubbles further increase their destructive effects on BF under ultrasound induction. Ultrasonic microbubbles can also carry the biologically active gas nitric oxide to promote the diffusion of BF and kill bacteria.[99] Low-frequency ultrasound (LFU) can accelerate the diffusion of tobumycin and significantly improve the overall inactivation efficiency of antimicrobials. Antibiotic treatment in combination with LFU increases the overall inactivation efficiency of BF to 80% within 120 minutes.[100]

### 4.15 Anti-BF infection effect of device surface materials

It has been reported that 70% of approximately 2 million hospital infections are triggered by the use of contaminated medical devices.[101] Medical implants (such as pacemakers, catheters, mechanical heart valves, etc.) are made of hydrophobic materials (polytetrafluoroethylene, stainless steel, silicon, etc.), and hydrophobic microorganisms are relatively easy to adhere to. They can change their adhesion properties and inhibit biofilm formation by applying anti-adhesion substances to their surfaces. The surface modification of medical devices mainly includes directly mixing antibacterial materials with raw materials to build medical devices with antibacterial surfaces, and in order to reduce bacterial adhesion and colonization by changing the surface hydrophilicity, conductivity, smoothness and other characteristics.[102] In view of the characteristics of medical implants, anti-adhesion substances are applied to the surface to change their adhesion properties and inhibit BF formation. It has been reported in the literature that the construction of bionic shark skin based on superhydrophobic polymers increases the surface roughness, along with the surface of bionic lotus leaves and the fluorine-containing antibacterial coating, which have ultra-low surface energy, can effectively prevent the adhesion of small objects such as proteins and bacteria on the surface, which can be used as a new strategy to inhibit bacterial adhesion.[103] Chitosan has strong anti-BF activity, and chitosan and its derivatives have been used to protect implantable medical devices from BF.[104]

### 4.16 Enhancement effect of antibiotics

Ciprofloxacin-copper complex dry powder was inhaled by mouse lung Pseudomonas aeruginosa biofilm infection models, the number of CFU in Pseudomonas aeruginosa was significantly decreased.[105] Hyperbaric oxygen therapy (HBOT) can enhance the efficacy of fluoroquinolones on Pseudomonas aeruginosa.[106] The use of benzamide-benzimidazole compounds can inhibit the Pseudomonas aeruginosa population induction regulator MvfR (PqsR), interfere with BF formation, and enhance the sensitivity of BF to antibiotics.[107]

### 4.17 Treatment measures for persistent bacteria

Attention should be paid to repeated infections caused by persisters. Antimicrobial peptide ZY4 can combat multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii infections, inhibit the floating growth and BF formation of Pseudomonas aeruginosa and acinetobacter baumannii, and ZY4 can kill Pseudomonas aeruginosa and acinetobacter baumannii persisters in a dose-dependent manner.[108]

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Aersileng contributed to the study conception, design and manuscript drafting; Junliang Li contributed to the study conception, guidance and review; Shengjun Cao and Lingfeng Wang contributed to the study conception and guidance.

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