Nanoparticle, a promising therapeutic strategy for the treatment of infective endocarditis

ABSTRACT

Infective endocarditis (IE) has been recognized as a biofilm-related disease caused by pathogenic microorganisms, such as bacteria and fungi that invade and damage the heart valves and endocardium. There are many difficulties and challenges in the antimicrobial treatment of IE, including multi-drug resistant pathogens, large dose of drug administration with following side effects, and poor prognosis. For the past few years, the development of nanotechnology has promoted the use of nanoparticles as antimicrobial nano-pharmaceuticals or novel drug delivery systems (NDDS) in antimicrobial therapy for chronic infections and biofilm-related infectious disease as these molecules exhibit several advantages. Therefore, nanoparticles have a potential role to play in solving problems in the treatment of IE, including improving antimicrobial activity, increasing drug bioavailability, minimizing frequency of drug administration, and preventing side effects. In this article, we review the latest advances in nanoparticles against drug-resistant bacteria in biofilm and recommends nanoparticles as an alternative strategy to the antibiotic treatment of IE.

Keywords: infective endocarditis, nanoparticles, nanotechnology, biofilm

INTRODUCTION

Nanotechnology is a novel method of producing and manipulating substance at the molecular scale, which can provide for more efficiently functioning mechanical, chemical, and biological components and bring great value to the development of medicine (1). The term “nano,” first presented by the famous material scientist Richard P. Feynman (2) in 1959, is a unit used to describe $10^{-9}$ of parameter in the microcosm. Over the past few years, nanotechnology has sparked intense interest among scientists and has been used to overcome biomedical difficulties and treat various diseases such as cancers (3), infectious diseases (4), and cardiovascular diseases (5). Nanoparticles, nano-carriers or nano-materials, defined as substances with a size of 1 to 100 nm, have specific functions at the cellular, atomic and molecular levels and are widely used in the fields of diagnosis and treatment of diseases (6). Nanoparticles or nano-carriers exhibit many advantages, including excellent drug stability and solubility, prolonged half-life of drug systemic circulation, stable and sustained drug-releasing rate, and lower frequency of drug administration, thus minimizing side effects of drug (6). As a result, they have become a promising alternative strategy to improve drug efficiency and minimize side effects in the treatment of diseases.

Infective endocarditis (IE) is an infectious disease defined by an infection of the heart valve and the endocardial surface, such as a prosthetic heart valve or an indwelling cardiac device (7). IE remains an infectious and life-threatening disease with an incidence of approximately 3–10 per 100,000 person-years (8, 9). With more prosthetic valve replacements or cardiac electronic device implantations performed for patients who suffer from heart valve diseases or arrhythmia, the incidence of IE is rising (8). IE is still a challenging disease bringing stupendous health and economic burden to the world.

With IE recognized as an infectious disease characterized by biofilm formation, the core of antimicrobial therapy for IE has focused on eradicating biofilm and drug-resistant bacteria. Nanoparticles, working as effectively functioning drugs
or novel drug delivery systems, are promising strategies for treating intractable and chronic infectious diseases, such as IE. For example, Omri et al. (10) developed nanocarriers encapsulating tobramycin to treat rats infected with *Pseudomonas aeruginosa* (*P. aeruginosa*). An *in vivo* study showed liposome-encapsulated tobramycin exhibited high pulmonary concentration and prolonged pulmonary retention than free tobramycin in the infected rats, which indicated that a nano-carrier had the potential in improving antibiotic availability. In this review, we provide a comprehensive description of the relationship between IE and biofilm and discuss the latest advances in nanoparticles in these fields.

**Infective endocarditis, an infectious disease related to biofilm formation**

The healthy cardiac endothelium has the ability to resist frequent bacteremia. However, when the endocardium is damaged by factors, such as rheumatic valvulitis, valve sclerosis, and direct bacterial activity; IE occurs with a series of pathological changes in the endocardium (11). In general, the typical pathological change observed in endocarditis is the occurrence of vegetation, which in essence is composed of microorganisms combined with platelet-rich thrombi and inflammatory leucocytes (7, 12, 13). The pathogenesis of endocarditis is described below. When the heart valve is injured, the injured endocardial surface promotes platelets and fibrin to form thrombi at the injury site. The microorganisms then accumulate and adhere to the thrombus, followed by the formation of microcolonies. Finally, with the accumulation of microcolonies, the vegetation biofilm becomes mature and causes embolization if it detaches from the biofilm (14).

Vegetation biofilm formation on the heart valve exerts a significant and noticeable effect on damage to the body. Vegetation biofilms physically affect the opening or closing of the heart valve, and then blood flow regurgitation or turbulence occurs (12, 14). However, general antibiotic therapy may not be able to destroy all the microorganisms that continuously detach from the vegetation biofilms (12, 14). As a result, more severe complications, such as heart failure and general infection, occur. Moreover, the dislodged biofilm or thrombus on the heart valve reaches the fine arteries through the blood circulation, leading to emboli in the peripheral circulation (12).

Clinicians did not recognize the bacterial growth mode as a “biofilm” for several years. In 1987, Marrie et al. (15) studied bacterial vegetation involving the aortic valves of 6 patients using microscopy and observed myriad microorganisms embedded in the matrix, indicating the presence of biofilm structures in endocarditis, although bacteria were negative upon culture. In essence, IE is an infectious disease associated with microorganism biofilm formation, and microorganisms directly cause tissue destruction and subsequent entry into deep structures of heart valve (13, 16). Several studies have shown that IE is associated with the formation of bacterial biofilms (17, 18). Bosio et al. (17) reported a clinical case of a patient with IE involving a porcine prosthetic aortic valve. Although vegetation or perforations were not detected in the valve, microscopic findings of histiocyte formation were observed along the endocardial surface of the valve. The presence of *Mycobacterium fortuitum*, a biofilm formation-associated mycobacterium, was finally detected in blood culture. Similarly, one case report documented the detection of biofilm formation associated with *M. fortuitum* on the prosthetic valves from patients with IE implanted with prosthetic valves; the *M. fortuitum* species are usually considered contaminants of the skin and mucosal membranes, which are capable of creating biofilms in implantation materials and thus cause infectious disease (18).

Most of the pathogenic bacteria that cause IE are involved in biofilm formation, such as *Staphylococcus* (19), *Streptococcus* (20), and *Enterococcus* species (21). Moreover, the species isolated from patients diagnosed with IE have the ability to create biofilms *in vitro* (22-24). IE differs from other infectious diseases because it is associated with biofilm formation on the endocardium. Parsek and Singh (14) summarized the features of clinical biofilm infection, including infecting microbes are always capable of attaching to the surface of the infected tissue and proliferating to form microcolonies; cell clusters or microcolonies encased in an extracellular matrix in the biofilm can be detected using microscopy; the infection is generally limited to a specific site in some cases and may undergo secondary dissemination; and biofilm is difficult to eradicate with antibiotics, although microbes in the planktonic state are susceptible. The microbes in a biofilm can serve as a reservoir and cause continuous infection (14). All these criteria are fulfilled in patients with IE.

**Mechanisms of drug resistance in biofilms of infective endocarditis**

**Biofilm as a permeation barrier**

A biofilm is composed of complex microcolonies of microorganisms combined with extracellular matrix (ECM) that is composed of polysaccharides, extracellular DNA (eDNA), and proteins, forming a gelatinous matrix that contributes to the adherence of biofilm to the damaged surface of the endocardium and the protection of microorganisms in the biofilm (22). Several studies have shown that barrier penetration plays a role in biofilm-associated drug resistance. The biofilm structures of *Staphylococcus aureus* (*S. aureus*) and *Staphylococcus epidermidis* (*S. epidermidis*) are capable of hindering the penetration of some antibiotics such as oxacillin, cefotaxime, and vancomycin; thus reducing the accumulation of bactericidal antibiotics in the entire biofilm (25).

Similarly, other drugs, including fluconazole and amphotericin B, diffuse very slowly through mixed-species biofilms of *Candida albicans* and *S. epidermidis* (26). Biofilm may func-
Transport proteins in the biofilm

The mechanism of recognizing and transporting substances through the bacterial membrane is responsible for antibiotic resistance. The proteins in bacterial membranes, such as efflux pumps and porins, function as carriers that recognize and transport substances, including antibiotics through the membrane (28). Efflux pumps, which are classified into six families, transport antibiotics out of the cell and participate in the extrusion of several types of antibiotics, such as acriflavine, chlorhexidine, and erythromycin (28, 33, 34). For example, the MacAB pump, a member of the ABC family, was identified to be involved in macrolide-specific resistance (33). The EmmdR pump, a member of the MATE family, is capable of pumping quinolones out of Enterobacter cloacae (35). Table 1 summarizes some efflux pumps from the six families described below.

Porins are the trimers of transmembrane β-barrels with water-filled channels for substance transportation, and they control the penetration of antibiotics through biofilms by permitting the selective small transport of hydrophilic molecules (28). Therefore, the deletion or mutation of porins may lead to multidrug resistance. For example, the mutation of porins such as OmpK36 in Klebsiella pneumonia is associated with nonenzymatic antibiotic resistance as the gene coding for the porin OmpK36 was downregulated in 56 extensively drug-resistant Klebsiella pneumonia samples (45).

Quorum sensing, horizontal gene transfer, and mutation in biofilms

Biofilms are considered a cooperative and commensal microbial group where microbial populations are surrounded by self-produced extracellular matrix and communicate with one another (50). Quorum sensing (QS) is a regulatory mechanism by which bacteria communicate through autoinducers, and QS contributes to biofilm recalcitrance (28). Autoinducers accumulating in the biofilm environment activate gene transcription. For instance, increased levels of autoinducers upregulate genes encoding some proteins involved in biofilm formation deep into the biofilm. Therefore, in the deeper cell layer, different gradients of oxygen and nutrients in the biofilm environment induce various physiological states of microorganisms (28). For example, an environment rich in oxygen and nutrients induces an aerobic state and fast growth, whereas a lack of oxygen and nutrients induces fermentation, slow growth, and dormant cells (28). In fact, the heterogeneity of the physiological state of cells is associated with tolerance to several antibiotics. Hypoxic conditions and nutrient dispersion reduce metabolic activity and shift cells in biofilms into a stationary phase-like state, thus conferring tolerance to antimicrobials that are most effective against actively growing bacteria (31). The biofilm is composed of different subpopulations with different susceptibilities to antibiotics, suggesting that biofilms containing different subpopulations are not likely to be susceptible to only one antibiotic. In the biofilm of P. aeruginosa, the cell population differentiates into different subpopulations with varying susceptibility to antibiotics (32). Cap-forming subpopulations are resistant to membrane-targeted antimicrobials, such as the cyclic cationic peptide mucin, whereas stem-forming subpopulations are sensitive to membrane-targeted antimicrobials (32). Researchers have postulated that biofilm resistance may result from poor susceptibility of subpopulations to antibiotics.

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development and virulence factors (28). In P. aeruginosa, QS is associated with biofilms. Davies et al. (47) studied the relationship between QS and biofilm formation in P. aeruginosa and found that LasI/LasR, the QS system, was necessary for the subsequent biofilm differentiation process. Therefore, the inhibition of QS circuits has been considered to be a potential strategy against biofilms. Virulence factors and biofilm formation can be inhibited by blocking QS (48).

Horizontal gene transfer (HGT), including conjugation, transformation, and transduction, plays an important role in the exchange of antimicrobial resistance (AMR) genes among bacteria. Biofilms provide a complex environment considered as a large reservoir of various resistance genes because AMR genes are disseminated among bacteria in biofilms (49). As a result, bacteria acquire the ability to adapt to changing environments in the presence of antibiotics through HGT. In biofilms, HGT is a potentially important factor leading to genetic diversity and multidrug resistance. The occurrence rate of HGT among bacteria appears higher in biofilms than in free-living bacteria. In S. aureus, the conjugation frequencies or transfer rate of the conjugative plasmid pG01 in biofilms is higher (up to 16000-fold) than that in planktonic cells (50).

Mutations in the bacterial genome are also associated with AMR (51). In biofilms from a chronic infection, mutations are common. The hypermutator phenotype of Pseudomonas in biofilms has been detected in patients who suffer from cystic fibrosis with chronic infections (52). Other bacteria such as S. aureus (53) and Haemophilus influenza (54) from patients with cystic fibrosis have also been reported to exhibit hypermutability. The resistance of biofilms to antibiotics is linked to gene mutations. For example, Francisella tularensis (F. tularensis) SCHU S4 acquired resistance to fluoroquinolone (FQ) because of the deletion of gene FupA that encodes a kind of protein required for iron uptake and bacterial virulence in F. tularensis (55).

**Main challenges in the antimicrobial therapy of infective endocarditis**

Drug resistance of biofilm in IE plays an important role in the antibiotic therapy, which may account for the failure of antimicrobial therapy. Microorganisms isolated from biofilms survive and multiply even when exposed to high concentrations of antibiotics (23) and exhibit a high level of resistance to antibiotics (56, 57). Di Domenico et al. (57) surgically obtained heart valve specimens from patients with IE and S. aureus, Enterococcus, and Streptococcus were isolated and identified *in vitro*. Clinical biofilm ring tests showed that S. aureus, Enterococcus, and Streptococcus were capable of producing biofilms *in vitro*, and these microbial isolates were resistant to most antimicrobial drugs such as ceftriaxone, gentamicin, levofloxacin, and vancomycin (57).

Effective antibiotic therapy for IE usually requires a large dose and a prolonged period of antibiotic administrations, usually several antibiotics in combination (9). Therefore, the selection of antibiotics to which the pathogens are sensitive and the period of antibiotic therapy seem very important in the management of IE because prolonged antibiotic therapy may increase the risk and toxicity to patients (9). High-dose aminoglycosides, such as gentamicin, administered over a long period as treatment IE are nephrotoxic and ototoxic (58, 59). These side effects undoubtedly are challenging for clinicians choosing antibiotics and course of treatment. Therefore, the most promising strategy for IE treatment is to target biofilms on the endocardium, inhibit bacterial adhesion, and disrupt bacterial architecture. Antimicrobial nanoparticles or nanocarriers have potential to decrease the need for repeated doses of antibiotics to overcome ineffectiveness and increase drug bioavailability, thus decreasing toxicity and side effects (60).

**Development of antimicrobial nanoparticles**

Currently, biofilm formation is considered as a point of drug resistance of chronic infection. Several diseases such as IE, C. albicans, and C. tropicalis, use biofilms for their survival and increase the antibiotic resistance (81, 82). In Table 2, we summarized some nanoparticles used against bacteria in biofilm to search for new tools to combat biofilm-associated diseases.

**Table 2. Some nanoparticles used against bacteria in biofilm**

| Drugs/nanoparticles | Targeted pathogens | Years | Author/reference |
|---------------------|--------------------|-------|------------------|
| **Metallic nanoparticles** |                     |       |                  |
| ZnO nanoparticle    | S. pneumoniae      | 2018  | Bhattacharyya et al. (70) |
| Copper oxide nanoparticle | S. lentus          | 2019  | Padmavathi et al. (71) |
| ZnO nanoparticle    | C. tropicalis      | 2017  | Jothiprakasam et al. (72) |
| Fe3O4 nanoparticle  | Candida             | 2018  | Salari et al. (73) |
| Selenium nanoparticle | S. aureus, P. aeruginosa, P. mirabilis | 2015 | Shakibaei et al. (74) |
| Silver nanoparticle | E. coli, P. aeruginosa | 2020 | Singh et al. (63) |
| Silver nanoparticle | Pseudomonas         | 2016  | Vyshnava et al. (75) |
| **Composite nanoparticle** |                     |       |                  |
| Biguanide-derived polymeric nanoparticle | MRSA | 2020 | Li et al. (76) |
| Zinc oxide nanoparticle coated by chitosan-linoleic acid | C. albicans | 2017 | Barad et al. (77) |
| Silver nanoparticles filled with polydimethylsiloxane | Vibrioaceae | 2016 | Yang et al. (78) |
| Chitosan-coated iron oxide nanoparticle | S. aureus | 2016 | Shi et al. (79) |
| Chitosan nanoparticle loading cellulobiose dehydrogenase and deoxyribonuclease I | C. albicans, S. aureus | 2020 | Tan et al. (80) |
| Cationic chitosan-pro polysaccharide nanoparticles | S. epidermidis | 2019 | Ong et al. (81) |
| Silk fibroin-silver nanoparticle | MRSA | 2013 | Fei et al. (82) |

C. albicans - Candida albicans; C. tropicalis - Candida tropicalis; E. coli - Escherichia coli; MRSA - methicillin-resistant Staphylococcus aureus; P. aeruginosa - Pseudomonas aeruginosa; P. salmonis - Piscirickettsia salmonis; P. mirabilis - Proteus mirabilis; S. aureus - Staphylococcus aureus; S. lentus - Staphylococcus lentus; S. epidermidis - Staphylococcus epidermidis.
Nanoparticles have been a great approach to combat drug-resistant microbes and for treatment of chronic and intractable infective diseases, such as tuberculosis (TB) because of their excellent and unique antimicrobial activity and function as drug delivery systems (66–68). The challenges of chronic and intractable infective disease remain the multi-drug resistance and side effects of drugs. Traditional antibiotics may be limited owing to their poor stability and solubility in blood, and the short half-life of drugs generally leads to increased frequency of drug administration and ensuing side effects. Mupirocin is an antibiotic with a unique mode of action. Because of its rapid elimination and poor solubility, the therapeutic use of mupirocin is limited to topical administration (69). Nanoparticles have been used as novel drug delivery systems to overcome these limitations. An experimental study on encapsulating mupirocin into nano-liposome was conducted and found that nano-mupirocin increased the half-life of mupirocin and enhanced therapeutic efficiency in treating mice necrotizing fasciitis (69). Table 2 summarizes some nanoparticles used against biofilms in recent years.

**Mechanism of action of antimicrobial nanoparticles**

**Metallic antimicrobial nanoparticles damage the membrane, thus increasing permeability**

Some nanoparticles directly interact with the bacterial cell wall and disturb the normal function of cells, thus killing microorganisms and inhibiting biofilm formation. Several metallic antimicrobial nanoparticles (NPs) such as silver NPs (AgNPs) (83), gold NPs (84), ZnO NPs (85, 86), and copper oxide NPs (71) inhibit the development of biofilms. For example, AgNPs is known to eradicate the biofilms of *Escherichia coli* (*E*. coli). The fatty acid content of *E*. coli cells is significantly decreased, suggesting that the integrity of the bacterial cell membrane is damaged by the AgNPs. In addition, membrane puncturing and cell lysis can be observed using electron microscopy (87).

The metallic antimicrobial nanoparticles are capable of inhibiting biofilm formation and killing bacteria through several mechanisms. Some metallic nanoparticles such as AgNPs and ZnO NPs, damage the membrane, thus increasing membrane permeability. AgNPs bind to, destabilize, and disrupt the cell membrane (88). A previous study showed that Zn⁺ from ZnO NPs interacts with the cell membrane, leading to reactive oxygen species (ROS) production and membrane disorganization (89). Metallic antimicrobial nanoparticles inhibit protein expressions and affect cellular functions. For example, Ag⁺ is capable of interacting with the ribosome band, inhibiting the expression of important enzymes and proteins required for ATP production (90). ZnO NPs inhibit cytosolic protein expression and the growth of *Bacillus subtilis* (*B*. *subtilis*) cell, thus affecting viability and biofilm formation (85).

**Nanoparticles carrying multiple antimicrobial agents as novel drug delivery systems exert synergistic effects**

Nanocarriers are transports used to function as novel drug delivery systems for several types of antibiotics, exerting a synergistic effect (66). The antimicrobial activity of nanocarriers mainly relies on the high surface area to volume ratio and the properties of various components they deliver (91). Nanoparticle-based drug delivery systems are capable of improving solubility and stability of drugs and prolonging drug circulation. Nanocarriers engineered to be activated by stimulating factors such as pH and ligands provide sustained and targeted drug release at the site of infection. In addition, nanoparticle-based drugs have been administrated in an effective manner to minimize the administration frequency and side effects, thus improving patient compliance (91–94).

Nanocarriers packaging multiple antimicrobial agents have significantly increased antimicrobial activity because they depend on the overall and synergistic functions of its active components (94–97). All components of nanoparticles exhibit synergistic actions, thereby improving the therapeutic value. Because few bacteria are resistant to all components of composite nanoparticles, composite nanoparticles are valuable treatments for resistant bacteria. Ruby (95) found that copper oxide nanoparticles synergistically combined with amoxiclav exhibit a significantly improved antimicrobial activity as the minimum inhibitory concentration of amoxiclav against *Proteus mirabilis* (*P*. *mirabilis*) and *S*. *aureus* was significantly reduced. Likewise, the efficacy of polymyxin B combined with AgNPs against *P*. *aeruginosa* biofilms was improved several times compared with unaided polymyxin B (98).

**Nanoparticles that increase uptake of the drug inside microbes**

Two types of nanoparticles, liposomes and dendrimers, increase the uptake of a drug inside microbes (66). The liposome is a spherical and loadable vesicle with a membrane composed of a lipid bilayer that is capable of carrying concentrated drugs and easily fusing with the cell membrane (66, 99). Therefore, antibiotics are easily delivered and released inside microbial cells, and the intracellular concentration of antibiotics would be increased owing to the fusion mechanism of liposomes. The intracellular concentration of antibiotics is increased, thus decreasing the requirement for high-dose antibiotics (100, 101). Neutral liposomes loaded with gentamicin improve the efficiency of antimicrobials, killing *P*. *aeruginosa* and *Klebsiella oxytoca* (*K*. *oxytoca*) at significantly lower concentrations than free gentamicin. The increased antibiotic activity is because of the fusion mechanism, namely the increased delivery of gentamicin to the bacterial cytoplasm (101).

Dendrimers are polymers that damage the cell membrane. The surface of dendrimers is positively charged and capable of binding to the negatively charged microbial cell membrane and increasing membrane permeability (66, 102).
Therefore, this mechanism enables a larger dose of antibiotics to penetrate microbial cells easily, thereby increasing the uptake of the drug into resistant bacteria (66). Backlund et al. (102) studied the efficiency of nitric oxide (NO) releasing dendrimers against Streptococcus biofilms. The dendrimer with a positively charged surface bound to the bacterial membrane through electrostatic interactions. The bactericidal efficacy was improved at pH 6.4 owing to the increased charge of the scaffold surface, promoting a more efficient interaction between the dendrimer and bacteria and damaging the cell membrane more effectively (102).

Nanoparticles that digest extracellular polymeric secretions, thus inhibiting biofilm formation

Some nanoparticles are designed and synthesized to digest the extracellular polymeric secretions (EPS) of biofilms. Nanoparticles loaded with enzymes such as pyruvate dehydrogenase and deoxyribonuclease (DNase) acquire the ability to digest components of the EPS of biofilms, thus disintegrating EPS and inhibiting biofilm formation. For example, Baelo et al. (103) developed nanoparticles combining ciprofloxacin with DNase I to eradicate P. aeruginosa biofilms. DNase I was capable of digesting eDNA, disassembling the structure of the bacterial ECM. As a result, the nanoparticles functionalized with ciprofloxacin and DNase I successfully prevented biofilm formation (103). Likewise, another composite nanoparticle delivering both oxacillin (Oxa) and DNase I (CSNP-DNase-Oxa) exhibits enhanced antibiofilm activity against S. aureus compared with Oxa-loaded nanoparticles without DNase and free Oxa (104). This enhanced antibiofilm activity is because of the DNase I, which disaggregates eDNA, thus inhibiting biofilm formation and eradicating mature biofilm more effectively (104).

Nanoparticles that precisely direct antimicrobial agents to the site of infection

Nanoparticles, working as drug delivery systems, release higher doses of antibiotics directly at the infected site and target the antimicrobial agents of biofilms in several ways (66). Targeted nanocarriers are activated by certain stimulating factors, such as ROS, low pH, or ligands in specific environments to exert directly on the biofilms (66). For example, Naha et al. (105) synthesized pH-responsive nannozymes, namely dextran-coated iron oxide nanoparticles. At a more acidic pH of the biofilm, for example 4.5, the nannozymes exhibited stronger catalytic activities, followed by the generation of large amounts of ROS that targeted the biofilm with high specificity in vivo. Likewise, Kalhapure et al. (106) developed pH-responsive solid lipid nanoparticles (SLNs) that were able to release and deliver vancomycin base (VM-FB) in an acidic environment. The pH-responsive SLNs released VM-FB significantly faster and exhibited an enhanced antimicrobial activity against methicillin-susceptible and resistant Staphylococcus aureus (MSSA and MRSA) respectively at pH 6.5 than at pH 7.4 (106). Similarly, pH-responsive lipid-dendrimer hybrid nanoparticles (LDH-NPs) delivering vancomycin (VCM) were developed by Maji et al. (107) and exhibited an increased release of VCM at the site of infection at pH 6.0.

Nanoparticles with the advantage of combating intracellular infection

Nanoparticles have the advantage of overcoming intracellular infection (108). Nanoparticles, such as liposomes, are easily phagocytosed by host phagocytes, thus increasing the concentration of intracellular antibiotics and killing the intracellular pathogens before they develop drug resistance (66, 109). Huang et al. (109) found that oleic acid (OA) loaded liposomes (LipoOAs) rapidly and easily fused with the bacterial membranes, contributing to transport inside cells. Therefore, LipoOA significantly increased the intracellular concentration and the potency of OA against MRSA than free OA (109). Scolari et al. (110) developed a chitosan and tween 80 (the neutral surfactant) decorated alginate nanoparticle encapsulating rifampicin and antioxidant ascorbic acid, which were mainly taken up by lung macrophages. Therefore, these nanoparticles are an important strategy to treat intracellular respiratory infections.

Recent development of nanoparticles or nanocarriers for treatment and prevention of infective endocarditis

The common pathogen of IE includes Viridans streptococci and S. aureus. At present, several antimicrobial nanoparticles have been developed against S. aureus biofilm and showed excellent antimicrobial activity. Miwu et al. (111) prepared sustained nitric oxide-releasing nanoparticles (NO-nanoparticles) against S. aureus biofilm formation to treat a rat central venous catheter (CVC) infection. NO released from NO-nanoparticles can kill bacteria by inactivating enzymes responsible for replication and reacting with oxygen to produce toxic species, and the NO-nanoparticles considerably and significantly reduced thicknesses and bacterial numbers in S. aureus biofilm compared to those in the control biofilm. This study showed that this kind nanoparticle was a promising way of treating S. aureus infections, such as IE (111). In addition, there is another study (69) on nano-mupirocin developed to enable parenteral activity by encapsulating nano-mupirocin in nano-liposome for the treatment of rabbit endocarditis. The encapsulation of nano-mupirocin into nano-liposome increased and prolonged mupirocin plasma level, whereas the free mupirocin showed a rapid elimination after administration. Nano-mupirocin treated animals had a significantly higher survival rate than those treated with free mupirocin (57% survival for nano-mupirocin vs. 0 for free mupirocin). The nano-mupirocin showed a better curative effect than free-mupirocin in the management of IE (69). Nanoparticles or nanomaterial have been also used to prevent prosthetic valve endocarditis. Antimicrobial nanoparticles have been reported to be applied to mechanical valves to prevent infection of prosthetic heart valves after heart valve replacement. Angelina et al. (112) coated the surface of pyrolytic carbon (PyC) on a prosthetic heart valve with a thin film of AgNPs to inhibit bacterial colonization. AgNPs are capable of interfering with the cell membrane and affecting bacterial viability. Furthermore, roughness at the nanoscale owing to the coating of AgNPs on the PyC heart valve surface contributes to preventing bacterial adherence to the surface (112). Therefore, nanoparticles with antimicrobial properties are capable of inhibiting bacterial growth, which shows a promising future for the use of nanoparticles for IE and other chronic infectious diseases.
However, many challenges in the application of antimicrobial nanoparticles in IE remain. Biocompatibility and safety of nanoparticles should be taken into consideration, although nanoparticles or nanocarriers provide hope for the treatment of various diseases (113). According to several studies, some nanoparticles are toxic or even carcinogenic (114–116). A nanomaterial termed carbon nanotubes (CNTs) potentially causes an asbestos-like mesothelioma hazard (114, 115). Gold nanoparticles of a particular size, which are widely used in several biomedical fields, may be toxic. Gold nanoparticles with a size 1.4 nm predominantly cause rapid cell death by necrosis, whereas gold particles of 15 nm are nontoxic up to 60-fold and 100-fold higher concentrations (116). Moreover, the biocompatibility of nanoparticles is associated with other characteristics, including the nanoparticle shape and structure, particle size, and surface properties (117). Therefore, biocompatibility of nanoparticles needs to be studied further before they are applied in vivo.

This study had several limitations. For instance, it was unclear whether the partial effect of antimicrobial nanoparticles on the infected heart valve could be influenced by high-speed blood flow and whether targeted nanocarriers could overcome shear stress of blood flow and adhere to the biofilm steadily or not, releasing antibiotics continuously.

CONCLUSION

As described above, IE is an infectious disease related to biofilm formation. One of difficult challenges of antimicrobial therapy of IE is antibiotic resistance and biofilm formation, and the key point of antimicrobial therapy for IE is to effectively and completely eradicate biofilms on heart valves and prevent the progress of severe infection. With the development of nanotechnology, application of nanoparticles has been an alternative strategy for treatment of IE. In this review, applications of several antimicrobial nanoparticles have been explored. Nanoparticles or nanocarriers exhibit various advantages of having excellent antimicrobial activity, combating drug-resistant microbes in the biofilm, decreasing frequency of drug administration, and minimizing side effects (6). Though there are various in vitro studies that show antimicrobial nanoparticles exhibit antimicrobial behavior against biofilm and drug-resistant microbes in the treatment of biofilm related diseases such as device-related biofilm infections and periodontitis (61, 118, 119), and a novel nanocarrier loading antibiotics is reported to improve the survival of rabbits suffering from IE (69). Further in vivo studies are needed to explore the therapeutic effects of antimicrobial nanoparticles on IE.

Overall, there is still a long road ahead for researchers to explore new and effective nanoparticles to be used in IE. The progress of nanoparticles against biofilm and drug-resistant microbes has greatly improved the therapy of biofilm-related infectious disease. With the development of nanotechnology, the prospect of nanoparticles in the treatment of IE is still promising and exciting.

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