THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

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

REVIEW

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

Qi Tong#
Tao Li#
Lu Jiang[1]
Zhengjie Wang
Yongjun Qian

Department of Cardiovascular Surgery, National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University; Chengdu-China
[1]Department of Cardiovascular Surgery, Sichuan Provincial People's University of Electronic Science and Technology of China; Chengdu-China

#These authors contribute equally to this work.

Corresponding Author:
Yongjun Qian
✉ qianyongjun@scu.edu.cn

Accepted: October 5, 2021
Available Online Date: February 2, 2022

Cite this article as: Tong Q, Li T, Jiang L, Wang Z, Qian Y. Nanoparticle, a promising therapeutic strategy for the treatment of infective endocarditis. Anatol J Cardiol 2022; 26: 90-9.

DOI: 10.5152/AnatolJCardiol.2021.867

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 *Micrococcus luteus* on the prosthetic valves from patients with IE implanted with prosthetic valves; the *Micrococcus* 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 microcopy; 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.

HIGHLIGHTS

- Infective endocarditis (IE) is an infectious disease of the heart valve, which is associated with biofilm formation.
- The core of antimicrobial therapy for IE is to eradicate biofilm and drug-resistant bacteria.
- Nanoparticles, working as effectively functioning drugs or novel drug delivery systems, have become promising strategies for treatment of 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-

tion as a barrier against antibiotics, which is related to drug resistance. However, the theory of resistance penetration does not completely explain the mechanisms of biofilm resistance to antibiotics. Biofilms appear to permit penetration of certain antibiotics. For instance, erythromycin penetrates *S. epidermidis* biofilms without completely killing the microbes (27). In addition, the function and effectiveness of antibiotics transport through biofilms are affected by components of the extracellular matrix (ECM), which has structural and protective functions (28). In studies on drug resistance in *P. aeruginosa*, alginate (29) and cyclic glucan (30) were shown to increase resistance to antimicrobials. Alginate contributes to increased microcolony formation and the formation of a thicker protective barrier (29). Cyclic glucan was proven to physically interact with cationic antibiotics such as aminoglycosides, thus protecting them from reaching microcolonies inside biofilm (30).

Complex diversity of biofilm environments

Biofilms provide a complex and diverse microenvironment with gradients of dispersion of nutrients, oxygen, pH, and metabolic waste. Oxygen and nutrients appear to be depleted by the cells close to the biofilm surface before they penetrate 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 induce 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.

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

Table 1. Summary of some efflux pumps and their substrates

Families of efflux pumps	Names of efflux pumps	Pathogens	Transport substrates
Multidrug and oxin extrusion (MATE)	YdhE (36)	*E. coli,*	Kanamycin, criflavin
	PmpM (37)	*P. aeruginosa*	Fluoroquinolones, fradiomycin, chlorhexidine
	AbeM (38)	*A. baumannii*	Norfloxacin, ciprofloxacin
Small multidrug resistance (SMDR),	EmrE (39)	*E. coli,*	Acriflavine
	Smr/QacC (40)	*S. aureus*	Acriflavine
Major facilitator (MF),			
	SdrM (41)	*S. aureus*	Norfloxacin, acriflavine
ATP-binding cassette (ABC),	Cdr1p, Cdr2p (42)	*C. albicans*	Terbinafine
Resistance nodulation division (RND)	acrAB (43)	*P. salmonis*	Florfenicol
Proteobacterial antimicrobial compound-efflux (PACE) families	AceI (44)	*A. baumannii*	Chlorhexidine

A. baumannii - Acinetobacter baumannii; C. albicans - Candida albicans; E. coli - Escherichia coli; P. aeruginosa - Pseudomonas aeruginosa; P. salmonis - Piscirickettsia salmonis; S. aureus - Staphylococcus aureus

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 pGO1 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, *Fraancisella 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,

Table 2. Some nanoparticles used against bactera 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	Shakibaie 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	*Vibrionaceae*	2016	Yang et al. (78)
Chitosan-coated iron oxide nanoparticle	*S. aureus*	2016	Shi et al. (79)
Chitosan nanoparticle loading cellobiose dehydrogenase and deoxyribonuclease I	*C. albicans, S. aureus*	2020	Tan et al. (80)
Cationic chitosan-propolis nanoparticle	*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

prosthetic implantation infection, and periodontitis are considered associated with biofilm formation (61). Treatment of biofilm-related diseases always require large dose and rapid frequency of drug administrations, thus producing side effects more than therapeutic effects. With the development of nanotechnology, nanoparticles and nanocarriers have caught the attention of scientists and have been used since 1990s (62). Several kinds of nanoparticles such as metallic nanoparticles and synthetic composite nanoparticles are used against biofilms (63-65).

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 multidrug 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 though 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 nanozymes, namely dextran-coated iron oxide nanoparticles. At a more acidic pH of the biofilm, for example 4.5, the nanozymes 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. Mihu 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 pyrolyric 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.

Acknowledgment: The authors acknowledge to Professor Zhiyong Qian (Professor of State Key Laboratory of Biotherapy, Sichuan University, the main research directions are nanobiotechnology, pharmacy, biomedical polymer materials, etc.) for improving our manuscript.

Institutional and financial support: This work was funded by the Scientific Research Project of National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (No. Z2018B19), and 1·3·5 project for disciplines of excellence–Clinical Research Incubation Project, West China Hospital, Sichuan University (No. 2019HXFH029), and Technology innovation research and development project of Chengdu Science and Technology Bureau (No. 2019-YF05-00183-SN), and the Major Science and Technology Project of Sichuan Province, China (No. 2021YFS0121), and the Science and Technology Project of Sichuan Province Health Commission, China (No. 21PJ035).

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Author contributions: Concept – Q.T., T.L., Y.Q.; Design – Q.T., T.L., L.J.; Supervision – L.J., Z.W., Y.Q.; Literature search – L.J., Z.W.; Writing – Q.T., T.L., Y.Q.; Critical review – Q.T., T.L., Z.W., Y.Q.

REFERENCES

1. Emerich DF, Thanos CG. Nanotechnology and medicine. Expert Opin Biol Ther 2003; 3: 655-63. [Crossref]
2. Feynman RP. There's plenty of room at the bottom. Journal of Microelectromechanical Systems 1992; 1: 60-6. [Crossref]
3. Chaturvedi VK, Singh A, Singh VK, Singh MP. Cancer Nanotechnology: A New Revolution for Cancer Diagnosis and Therapy. Curr Drug Metab 2019; 20: 416-29. [Crossref]
4. Liu Y, Shi L, Su L, van der Mei HC, Jutte PC, Ren Y, et al. Nanotechnology-based antimicrobials and delivery systems for biofilm-infection control. Chem Soc Rev 2019; 48: 428-46. [Crossref]
5. Palazzolo JS, Westein E, Hagemeyer CE, Wang TY. Targeting Nanotechnologies for the Treatment of Thrombosis and Cardiovascular Disease. Semin Thromb Hemost 2020; 46: 606-21.[Crossref]
6. Zhang L, Gu FX, Chan JM, Wang AZ, Langer RS, Farokhzad OC. Nanoparticles in medicine: therapeutic applications and developments. Clin Pharmacol Ther 2008; 83: 761-9. [Crossref]
7. Cahill TJ, Prendergast BD. Infective endocarditis. Lancet 2016; 387: 882-93. [Crossref]
8. Jensen AD, Bundgaard H, Butt JH, Bruun NE, Voldstedlund M, Torp-Pedersen C, et al. Temporal changes in the incidence of infective endocarditis in Denmark 1997-2017: A nationwide study. Int J Cardiol 2021; 326: 145-52. [Crossref]
9. Cahill TJ, Baddour LM, Habib G, Hoen B, Salaun E, Pettersson GB, et al. Challenges in Infective Endocarditis. J Am Coll Cardiol 2017; 69: 325-44. [Crossref]
10. Omri A, Beaulac C, Bouhajib M, Montplaisir S, Sharkawi M, Lagacé J. Pulmonary retention of free and liposome-encapsulated tobramycin after intratracheal administration in uninfected rats and rats infected with Pseudomonas aeruginosa. Antimicrob Agents Chemother 1994; 38: 1090-5. [Crossref]
11. Werdan K, Dietz S, Löffler B, Niemann S, Bushnaq H, Silber RE, et al. Mechanisms of infective endocarditis: pathogen-host interaction and risk states. Nat Rev Cardiol 2014; 11: 35-50. [Crossref]
12. Vestby LK, Grønseth T, Simm R, Nesse LL. Bacterial Biofilm and its Role in the Pathogenesis of Disease. Antibiotics (Basel) 2020; 9: 59. [Crossref]
13. Del Pozo JL. Biofilm-related disease. Expert Rev Anti Infect Ther 2018; 16: 51-65. [Crossref]
14. Parsek MR, Singh PK. Bacterial biofilms: an emerging link to disease pathogenesis. Annu Rev Microbiol 2003; 57: 677-701. [Crossref]
15. Marrie TJ, Cooper JH, Costerton JW. Ultrastructure of cardiac bacterial vegetations on native valves with emphasis on alterations in bacterial morphology following antibiotic treatment. Can J Cardiol 1987; 3: 275-80.

16. Afonina I, Lim XN, Tan R, Kline KA. Planktonic Interference and Biofilm Alliance between Aggregation Substance and Endocarditis- and Biofilm-Associated Pili in Enterococcus faecalis. J Bacteriol 2018; 200: e00361-18. [Crossref]
17. Bosio S, Leekha S, Gamb SI, Wright AJ, Terrell CL, Miller DV. Mycobacterium fortuitum prosthetic valve endocarditis: a case for the pathogenetic role of biofilms. Cardiovasc Pathol 2012; 21: 361-4. [Crossref]
18. Rodriguez-Nava G, Mohamed A, Yanez-Bello MA, Trelles-Garcia DP. Advances in medicine and positive natural selection: Prosthetic valve endocarditis due to biofilm producer Micrococcus luteus. IDCases 2020; 20: e00743. [Crossref]
19. Paharik AE, Horswill AR. The Staphylococcal Biofilm: Adhesins, Regulation, and Host Response. Microbiol Spectr 2016; 4: 10.1128/microbiolspec.VMBF-0022-2015. [Crossref]
20. Domenech M, García E, Moscoso M. Biofilm formation in Streptococcus pneumoniae. Microb Biotechnol 2012; 5: 455-65. [Crossref]
21. Mohamed JA, Huang DB. Biofilm formation by enterococci. J Med Microbiol 2007; 56: 1581-8. [Crossref]
22. Elgharably H, Hussain ST, Shrestha NK, Blackstone EH, Pettersson GB. Current Hypotheses in Cardiac Surgery: Biofilm in Infective Endocarditis. Semin Thorac Cardiovasc Surg 2016; 28: 56-9. [Crossref]
23. Presterl E, Grisold AJ, Reichmann S, Hirschl AM, Georgopoulos A, Graninger W. Viridans streptococci in endocarditis and neutropenic sepsis: biofilm formation and effects of antibiotics. J Antimicrob Chemother 2005; 55: 45-50. [Crossref]
24. Presterl E, Lassnigg A, Eder M, Reichmann S, Hirschl AM, Graninger W. Effects of tigecycline, linezolid and vancomycin on biofilms of viridans streptococci isolates from patients with endocarditis. Int J Artif Organs 2007; 30: 798-804. [Crossref]
25. Singh R, Ray P, Das A, Sharma M. Penetration of antibiotics through Staphylococcus aureus and Staphylococcus epidermidis biofilms. J Antimicrob Chemother 2010; 65: 1955-8. [Crossref]
26. Al-Fattani MA, Douglas LJ. Penetration of Candida biofilms by antifungal agents. Antimicrob Agents Chemother 2004; 48: 3291-7. [Crossref]
27. Lin MH, He L, Gao J, Liu YX, Suo JJ, Xing YB, et al. Penetration of erythromycin through Staphylococcus epidermidis biofilm. Chin Med J (Engl) 2013; 126: 2647-51.
28. Uruén C, Chopo-Escuin G, Tommassen J, Mainar-Jaime RC, Arenas J. Biofilms as Promoters of Bacterial Antibiotic Resistance and Tolerance. Antibiotics (Basel) 2020; 10: 3. [Crossref]
29. Hentzer M, Teitzel GM, Balzer GJ, Heydorn A, Molin S, Givskov M, et al. Alginate overproduction affects Pseudomonas aeruginosa biofilm structure and function. J Bacteriol 2001; 183: 5395-401. [Crossref]
30. Sadovskaya I, Vinogradov E, Li J, Hachani A, Kowalska K, Filloux A. High-level antibiotic resistance in Pseudomonas aeruginosa biofilm: the ndvB gene is involved in the production of highly glycerol-phosphorylated beta-(1->3)-glucans, which bind aminoglycosides. Glycobiology 2010; 20: 895-904. [Crossref]
31. Borriello G, Werner E, Roe F, Kim AM, Ehrlich GD, Stewart PS. Oxygen limitation contributes to antibiotic tolerance of Pseudomonas aeruginosa in biofilms. Antimicrob Agents Chemother 2004; 48: 2659-64. [Crossref]
32. Haagensen JA, Klausen M, Ernst RK, Miller SI, Folkesson A, Tolker-Nielsen T, et al. Differentiation and distribution of colistin- and sodium dodecyl sulfate-tolerant cells in Pseudomonas aeruginosa biofilms. J Bacteriol 2007; 189: 28-37. [Crossref]
33. Kobayashi N, Nishino K, Yamaguchi A. Novel macrolide-specific ABC-type efflux transporter in Escherichia coli. J Bacteriol 2001; 183: 5639-44. [Crossref]
34. Hassan KA, Liu Q, Henderson PJ, Paulsen IT. Homologs of the Acinetobacter baumannii AceI transporter represent a new family of bacterial multidrug efflux systems. mBio 2015; 6: e01982-14. [Crossref]
35. He GX, Thorpe C, Walsh D, Crow R, Chen H, Kumar S, et al. EmdR, a new member of the MATE family of multidrug transporters, extrudes quinolones from Enterobacter cloacae. Arch Microbiol 2011; 193: 759-65. [Crossref]
36. Morita Y, Kodama K, Shiota S, Mine T, Kataoka A, Mizushima T, et al. NorM, a putative multidrug efflux protein, of Vibrio parahaemolyticus and its homolog in Escherichia coli. Antimicrob Agents Chemother 1998; 42: 1778-82. [Crossref]
37. He GX, Kuroda T, Mima T, Morita Y, Mizushima T, Tsuchiya T. An H(+)-coupled multidrug efflux pump, PmpM, a member of the MATE family of transporters, from Pseudomonas aeruginosa. J Bacteriol 2004; 186: 262-5. [Crossref]
38. Su XZ, Chen J, Mizushima T, Kuroda T, Tsuchiya T. AbeM, an H+-coupled Acinetobacter baumannii multidrug efflux pump belonging to the MATE family of transporters. Antimicrob Agents Chemother 2005; 49: 4362-4. [Crossref]
39. Saleh M, Bay DC, Turner RJ. Few Conserved Amino Acids in the Small Multidrug Resistance Transporter EmrE Influence Drug Polyselectivity. Antimicrob Agents Chemother 2018; 62: e00461-18. [Crossref]
40. Paulsen IT, Brown MH, Dunstan SJ, Skurray RA. Molecular characterization of the staphylococcal multidrug resistance export protein QacC. J Bacteriol 1995; 177: 2827-33. [Crossref]
41. Yamada Y, Hideka K, Shiota S, Kuroda T, Tsuchiya T. Gene cloning and characterization of SdrM, a chromosomally-encoded multidrug efflux pump, from Staphylococcus aureus. Biol Pharm Bull 2006; 29: 554-6. [Crossref]
42. Schuetzer-Muehlbauer M, Willinger B, Egner R, Ecker G, Kuchler K. Reversal of antifungal resistance mediated by ABC efflux pumps from Candida albicans functionally expressed in yeast. Int J Antimicrob Agents 2003; 22: 291-300. [Crossref]
43. Sandoval R, Oliver C, Valdivia S, Valenzuela K, Haro RE, Sánchez P, et al. Resistance-nodulation-division efflux pump acrAB is modulated by florfenicol and contributes to drug resistance in the fish pathogen Piscirickettsia salmonis. FEMS Microbiol Lett 2016; 363: fnw102. [Crossref]
44. Bolla JR, Howes AC, Fiorentino F, Robinson CV. Assembly and regulation of the chlorhexidine-specific efflux pump AceI. Proc Natl Acad Sci U S A 2020; 117: 17011-8. [Crossref]
45. Vuotto C, Longo F, Pascolini C, Donelli G, Balice MP, Libori MF, et al. Biofilm formation and antibiotic resistance in Klebsiella pneumoniae urinary strains. J Appl Microbiol 2017; 123: 1003-18. [Crossref]
46. Solano C, Echeverz M, Lasa I. Biofilm dispersion and quorum sensing. Curr Opin Microbiol 2014; 18: 96-104. [Crossref]
47. Davies DG, Parsek MR, Pearson JP, Iglewski BH, Costerton JW, Greenberg EP. The involvement of cell-to-cell signals in the development of a bacterial biofilm. Science 1998; 280: 295-8. [Crossref]
48. O'Loughlin CT, Miller LC, Siryaporn A, Drescher K, Semmelhack MF, Bassler BL. A quorum-sensing inhibitor blocks Pseudomonas aeruginosa virulence and biofilm formation. Proc Natl Acad Sci U S A 2013; 110: 17981-6. [Crossref]
49. Olsen I. Biofilm-specific antibiotic tolerance and resistance. Eur J Clin Microbiol 2015; 34: 877-86. [Crossref]
50. Savage VJ, Chopra I, O'Neill AJ. Staphylococcus aureus Biofilms Promote Horizontal Transfer of Antibiotic Resistance. Antimicrob Agents Chemother 2013; 57: 1968-70. [Crossref]
51. Woodford N, Ellington MJ. The emergence of antibiotic resistance by mutation. Clin Microbiol Infect 2007; 13: 5-18. [Crossref]
52. Maciá MD, Blanquer D, Togores B, Sauleda J, Pérez JL, Oliver A. Hypermutation is a key factor in development of multiple-antimicrobial resistance in Pseudomonas aeruginosa strains causing

chronic lung infections. Antimicrob Agents Chemother 2005; 49: 3382-6. [Crossref]
53. Prunier AL, Malbruny B, Laurans M, Brouard J, Duhamel JF, Leclercq R. High rate of macrolide resistance in Staphylococcus aureus strains from patients with cystic fibrosis reveals high proportions of hypermutable strains. J Infect Dis 2003; 187: 1709-16. [Crossref]
54. Román F, Cantón R, Pérez-Vázquez M, Baquero F, Campos J. Dynamics of long-term colonization of respiratory tract by Haemophilus influenzae in cystic fibrosis patients shows a marked increase in hypermutable strains. J Clin Microbiol 2004; 42: 1450-9. [Crossref]
55. Siebert C, Lindgren H, Ferré S, Villers C, Boisset S, Perard J, et al. Francisella tularensis: FupA mutation contributes to fluoroquinolone resistance by increasing vesicle secretion and biofilm formation. Emerg Microbes Infect 2019; 8: 808-22. [Crossref]
56. Chifiriuc MC, Banu O, Bleotu C, Lazar V. Interaction of bacteria isolated from clinical biofilms with cardiovascular prosthetic devices and eukaryotic cells. Anaerobe 2011; 17: 419-21. [Crossref]
57. Di Domenico EG, Rimoldi SG, Cavallo I, D'Agosto G, Trento E, Cagnoni G, et al. Microbial biofilm correlates with an increased antibiotic tolerance and poor therapeutic outcome in infective endocarditis. BMC Microbiol 2019; 19: 228. [Crossref]
58. Cosgrove SE, Vigliani GA, Fowler VG Jr, Abrutyn E, Corey GR, Levine DP, et al. Initial low-dose gentamicin for Staphylococcus aureus bacteremia and endocarditis is nephrotoxic. Clin Infect Dis 2009; 48: 713-21. [Crossref]
59. Selimoglu E. Aminoglycoside-induced ototoxicity. Curr Pharm Des 2007; 13: 119-26.[Crossref]
60. Namdari M, Eatemadi A, Soleimaninejad M, Hammed AT. A brief review on the application of nanoparticle enclosed herbal medicine for the treatment of infective endocarditis. Biomed Pharmacother 2017; 87: 321-31. [Crossref]
61. Jamal M, Ahmad W, Andleeb S, Jalil F, Imran M, Nawaz MA, et al. Bacterial biofilm and associated infections. J Chin Med Assoc 2018; 81: 7-11. [Crossref]
62. Anselmo AC, Mitragotri S. Nanoparticles in the clinic: An update. Bioeng Transl Med 2019; 4: e10143. [Crossref]
63. Singh P, Pandit S, Mokkapati V, Garnaes J, Mijakovic I. A Sustainable Approach for the Green Synthesis of Silver Nanoparticles from Solibacillus isronensis sp. and Their Application in Biofilm Inhibition. Molecules 2020; 25: 2783. [Crossref]
64. Weldrick PJ, Iveson S, Hardman MJ, Paunov VN. Breathing new life into old antibiotics: overcoming antibacterial resistance by antibiotic-loaded nanogel carriers with cationic surface functionality. Nanoscale 2019; 11: 10472-85. [Crossref]
65. Han CD, Goodwine J, Romero N, Steck KS, Sauer K, Doiron A. Enzyme-encapsulating polymeric nanoparticles: A potential adjunctive therapy in Pseudomonas aeruginosa biofilm-associated infection treatment. Colloids Surf B Biointerfaces 2019; 184: 110512. [Crossref]
66. Pelgrift RY, Friedman AJ. Nanotechnology as a therapeutic tool to combat microbial resistance. Adv Drug Deliv Rev 2013; 65: 1803-15. [Crossref]
67. Tăbăran AF, Matea CT, Mocan T, Tăbăran A, Mihaiu M, Iancu C, et al. Silver Nanoparticles for the Therapy of Tuberculosis. Int J Nanomedicine 2020; 15: 2231-58. [Crossref]
68. Yeh YC, Huang TH, Yang SC, Chen CC, Fang JY. Nano-Based Drug Delivery or Targeting to Eradicate Bacteria for Infection Mitigation: A Review of Recent Advances. Front Chem 2020; 8: 286. [Crossref]
69. Cern A, Michael-Gayego A, Bavli Y, Korena E, Goldblum A, Moses AE, et al. Nano-mupirocin: enabling the parenteral activity of mupirocin. Eur J Nanomed 2016; 8: 139-49. [Crossref]
70. Bhattacharyya P, Agarwal B, Goswami M, Maiti D, Baruah S, Tribedi P. Zinc oxide nanoparticle inhibits the biofilm formation of Streptococcus pneumoniae. Antonie Van Leeuwenhoek 2018; 111: 89-99. [Crossref]
71. Padmavathi AR, Sriyutha Murthy P, Das A, Nishad PA, Pandian R, Rao TS. Copper oxide nanoparticles as an effective anti-biofilm agent against a copper tolerant marine bacterium, Staphylococcus lentus. Biofouling 2019; 35: 1007-25. [Crossref]
72. Jothiprakasam V, Sambantham M, Chinnathambi S, Vijayaboopathi S. Candida tropicalis biofilm inhibition by ZnO nanoparticles and EDTA. Arch Oral Biol 2017; 73: 21-4. [Crossref]
73. Salari S, Sadat Seddighi N, Ghasemi Nejad Almani P. Evaluation of biofilm formation ability in different Candida strains and anti-biofilm effects of Fe3O4-NPs compared with Fluconazole: an in vitro study. J Mycol Med 2018; 28: 23-8. [Crossref]
74. Shakibaie M, Forootanfar H, Golkari Y, Mohammadi-Khorsand T, Shakibaie MR. Anti-biofilm activity of biogenic selenium nanoparticles and selenium dioxide against clinical isolates of Staphylococcus aureus, Pseudomonas aeruginosa, and Proteus mirabilis. J Trace Elem Med Biol 2015; 29: 235-41. [Crossref]
75. Vyshnava SS, Kanderi DK, Panjala SP, Pandian K, Bontha RR, Goukanapalle PK, et al. Effect of Silver Nanoparticles Against the Formation of Biofilm by Pseudomonas aeruginosa an In silico Approach. Appl Biochem Biotechnol 2016; 180: 426-37. [Crossref]
76. Li J, Zhong W, Zhang K, Wang D, Hu J, Chan-Park MB. Biguanide-Derived Polymeric Nanoparticles Kill MRSA Biofilm and Suppress Infection In Vivo. ACS Appl Mater Interfaces 2020; 12: 21231-41. [Crossref]
77. Barad S, Roudbary M, Omran AN, Daryasari MP. Preparation and characterization of ZnO nanoparticles coated by chitosan-linoleic acid; fungal growth and biofilm assay. Bratisl Med J 2017; 118: 169-74. [Crossref]
78. Yang JL, Li YF, Liang X, Guo XP, Ding DW, Zhang D, et al. Silver Nanoparticles Impact Biofilm Communities and Mussel Settlement. Sci Rep 2016; 6: 37406. [Crossref]
79. Shi SF, Jia JF, Guo XK, Zhao YP, Chen DS, Guo YY, et al. Reduced Staphylococcus aureus biofilm formation in the presence of chitosan-coated iron oxide nanoparticles. Int J Nanomed 2016; 11: 6499-506. [Crossref]
80. Tan Y, Ma S, Leonhard M, Moser D, Ludwig R, Schneider-Stickler B. Co-immobilization of cellobiose dehydrogenase and deoxyribonuclease I on chitosan nanoparticles against fungal/bacterial polymicrobial biofilms targeting both biofilm matrix and microorganisms. Mater Sci Eng C Mater Biol Appl 2020; 108: 110499. [Crossref]
81. Ong TH, Chitra E, Ramamurthy S, Ling CCS, Ambu SP, Davamani F. Cationic chitosan-propolis nanoparticles alter the zeta potential of S. epidermidis, inhibit biofilm formation by modulating gene expression and exhibit synergism with antibiotics. PLoS One 2019; 14: e0213079. [Crossref]
82. Fei X, Jia M, Du X, Yang Y, Zhang R, Shao Z, et al. Green synthesis of silk fibroin-silver nanoparticle composites with effective antibacterial and biofilm-disrupting properties. Biomacromolecules 2013; 14: 4483-8. [Crossref]
83. Siddique MH, Aslam B, Imran M, Ashraf A, Nadeem H, Hayat S, et al. Effect of Silver Nanoparticles on Biofilm Formation and EPS Production of Multidrug-Resistant Klebsiella pneumoniae. Biomed Res Int 2020; 2020: 6398165. [Crossref]
84. Ahiwale SS, Bankar AV, Tagunde S, Kapadnis BP. A Bacteriophage Mediated Gold Nanoparticles Synthesis and Their Anti-biofilm Activity. Indian J Microbiol 2017; 57: 188-94. [Crossref]
85. Hsueh YH, Ke WJ, Hsieh CT, Lin KS, Tzou DY, Chiang CL. ZnO Nanoparticles Affect Bacillus subtilis Cell Growth and Biofilm Formation. PLoS One 2015; 10: e0128457. [Crossref]

86. Lee JH, Kim YG, Cho MH, Lee J. ZnO nanoparticles inhibit Pseudomonas aeruginosa biofilm formation and virulence factor production. Microbiol Res 2014; 169: 888-96. [Crossref]
87. Estevez MB, Raffaelli S, Mitchell SG, Faccio R, Alborés S. Biofilm Eradication Using Biogenic Silver Nanoparticles. Molecules 2020; 25: 2023. [Crossref]
88. Lara HH, Ayala-Nunez NV, Turrent LDI, Padilla CR. Bactericidal effect of silver nanoparticles against multidrug-resistant bacteria. World J Microb Biot 2010; 26: 615-21. [Crossref]
89. Huang Z, Zheng X, Yan D, Yin G, Liao X, Kang Y, et al. Toxicological effect of ZnO nanoparticles based on bacteria. Langmuir 2008; 24: 4140-4. [Crossref]
90. Yamanaka M, Hara K, Kudo J. Bactericidal actions of a silver ion solution on Escherichia coli, studied by energy-filtering transmission electron microscopy and proteomic analysis. Appl Environ Microbiol 2005; 71: 7589-93. [Crossref]
91. Huh AJ, Kwon YJ. "Nanoantibiotics": a new paradigm for treating infectious diseases using nanomaterials in the antibiotics resistant era. J Control Release 2011; 156: 128-45. [Crossref]
92. Sosnik A, Carcaboso AM, Glisoni RJ, Moretton MA, Chiappetta DA. New old challenges in tuberculosis: potentially effective nanotechnologies in drug delivery. Adv Drug Deliv Rev 2010; 62: 547-59. [Crossref]
93. Abdel Raheem IA, Abdul Razek A, Elgendy AA, Saleh NM, Shaaban MI, Abd El-Hady FK. Design, Evaluation And Antimicrobial Activity Of Egyptian Propolis-Loaded Nanoparticles: Intrinsic Role As A Novel And Naturally Based Root Canal Nanosealer. Int J Nanomedicine 2019; 14: 8379-98. [Crossref]
94. Girish VM, Liang H, Aguilan JT, Nosanchuk JD, Friedman JM, Nacharaju P. Anti-biofilm activity of garlic extract loaded nanoparticles. Nanomedicine 2019; 20: 102009. [Crossref]
95. Arul Selvaraj RC, Rajendran M, Nagaiah HP. Re-Potentiation of beta-Lactam Antibiotic by Synergistic Combination with Biogenic Copper Oxide Nanocubes against Biofilm Forming Multidrug-Resistant Bacteria. Molecules 2019; 24: 3055. [Crossref]
96. Kamble SP, Shinde KD. Anti-biofilm Activity Against Gram-Positive Bacteria by Biologically Synthesized Silver Nanoparticles Using Curcuma longa. Pharm Nanotechnol 2018; 6: 165-70. [Crossref]
97. Patel KK, Tripathi M, Pandey N, Agrawal AK, Gade S, Anjum MM, et al. Alginate lyase immobilized chitosan nanoparticles of ciprofloxacin for the improved antimicrobial activity against the biofilm associated mucoid P. aeruginosa infection in cystic fibrosis. Int J Pharm 2019; 563: 30-42. [Crossref]
98. Salman M, Rizwana R, Khan H, Munir I, Hamayun M, Iqbal A, et al. Synergistic effect of silver nanoparticles and polymyxin B against biofilm produced by Pseudomonas aeruginosa isolates of pus samples in vitro. Artif Cells Nanomed Biotechnol 2019; 47: 2465-72. [Crossref]
99. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nat Rev Drug Discov 2005; 4: 145-60. [Crossref]
100. Huang CM, Chen CH, Pornpattananangkul D, Zhang L, Chan M, Hsieh MF, et al. Eradication of drug resistant Staphylococcus aureus by liposomal oleic acids. Biomaterials 2011; 32: 214-21. [Crossref]
101. Alhariri M, Majrashi MA, Bahkali AH, Almajed FS, Azghani AO, Khiyami MA, et al. Efficacy of neutral and negatively charged liposome-loaded gentamicin on planktonic bacteria and biofilm communities. Int J Nanomedicine 2017; 12: 6949-61. [Crossref]
102. Backlund CJ, Worley BV, Schoenfisch MH. Anti-biofilm action of nitric oxide-releasing alkyl-modified poly(amidoamine) dendrimers against Streptococcus mutans. Acta Biomater 2016; 29: 198-205. [Crossref]
103. Baelo A, Levato R, Julián E, Crespo A, Astola J, Gavaldà J, et al. Disassembling bacterial extracellular matrix with DNase-coated nanoparticles to enhance antibiotic delivery in biofilm infections. J Control Release 2015; 209: 150-8. [Crossref]
104. Tan YL, Ma S, Leonhard M, Moser D, Haselmann GM, Wang J, et al. Enhancing antibiofilm activity with functional chitosan nanoparticles targeting biofilm cells and biofilm matrix. Carbohydr Polym 2018; 200: 35-42. [Crossref]
105. Naha PC, Liu Y, Hwang G, Huang Y, Gubara S, Jonnakuti V, et al. Dextran-Coated Iron Oxide Nanoparticles as Biomimetic Catalysts for Localized and pH-Activated Biofilm Disruption. ACS Nano 2019; 13: 4960-71. [Crossref]
106. Kalhapure RS, Sikwal DR, Rambharose S, Mocktar C, Singh S, Bester L, et al. Enhancing targeted antibiotic therapy via pH responsive solid lipid nanoparticles from an acid cleavable lipid. Nanomedicine 2017; 13: 2067-77. [Crossref]
107. Maji R, Omolo CA, Agrawal N, Maduray K, Hassan D, Mokhtar C, et al. pH-Responsive Lipid-Dendrimer Hybrid Nanoparticles: An Approach To Target and Eliminate Intracellular Pathogens. Mol Pharm 2019; 16: 4594-609. [Crossref]
108. Heiro M, Helenius H, Makila S, Hohenthal U, Savunen T, Engblom E, et al. Infective endocarditis in a Finnish teaching hospital: a study on 326 episodes treated during 1980-2004. Heart 2006; 92: 1457-62. [Crossref]
109. Huang CM, Chen CH, Pornpattananangkul D, Zhang L, Chan M, Hsieh MF, et al. Eradication of drug resistant Staphylococcus aureus by liposomal oleic acids. Biomaterials 2011; 32: 214-21. [Crossref]
110. Scolari IR, Volpini X, Fanani ML, La Cruz-Thea B, Natali L, Musri MM, et al. Exploring the Toxicity, Lung Distribution, and Cellular Uptake of Rifampicin and Ascorbic Acid-Loaded Alginate Nanoparticles as Therapeutic Treatment of Lung Intracellular Infections. Mol Pharm 2021; 18: 807-21. [Crossref]
111. Mihu MR, Cabral V, Pattabhi R, Tar MT, Davies KP, Friedman AJ, et al. Sustained Nitric Oxide-Releasing Nanoparticles Interfere with Methicillin-Resistant Staphylococcus aureus Adhesion and Biofilm Formation in a Rat Central Venous Catheter Model. Antimicrob Agents Chemother 2017; 61: e02020-16. [Crossref]
112. Angelina JTT, Ganesan S, Panicker TMR, Narayani R, Korath MP, Jagadeesan K. Pulsed laser deposition of silver nanoparticles on prosthetic heart valve material to prevent bacterial infection. Materials Technology 2017; 32: 148-55. [Crossref]
113. Wolfram J, Zhu M, Yang Y, Shen J, Gentile E, Paolino D, et al. Safety of Nanoparticles in Medicine. Curr Drug Targets 2015; 16: 1671-81. [Crossref]
114. Murphy FA, Poland CA, Duffin R, Donaldson K. Length-dependent pleural inflammation and parietal pleural responses after deposition of carbon nanotubes in the pulmonary airspaces of mice. Nanotoxicology 2013; 7: 1157-67. [Crossref]
115. Donaldson K, Murphy FA, Duffin R, Poland CA. Asbestos, carbon nanotubes and the pleural mesothelium: a review of the hypothesis regarding the role of long fibre retention in the parietal pleura, inflammation and mesothelioma. Part Fibre Toxicol 2010; 7: 5. [Crossref]
116. Pan Y, Neuss S, Leifert A, Fischler M, Wen F, Simon U, et al. Size-dependent cytotoxicity of gold nanoparticles. Small 2007; 3: 1941-9. [Crossref]
117. Tang FQ, Li LL, Chen D. Mesoporous Silica Nanoparticles: Synthesis, Biocompatibility and Drug Delivery. Adv Mater 2012; 24: 1504-34. [Crossref]
118. Qi M, Li X, Sun X, Li C, Tay FR, Weir MD, et al. Novel nanotechnology and near-infrared photodynamic therapy to kill periodontitis-related biofilm pathogens and protect the periodontium. Dent Mater 2019; 35: 1665-81. [Crossref]
119. Azevedo MM, Ramalho P, Silva AP, Teixeira-Santos R, Pina-Vaz C, Rodrigues AG. Polyethyleneimine and polyethyleneimine-based nanoparticles: novel bacterial and yeast biofilm inhibitors. J Med Microbiol 2014; 63: 1167-73. [Crossref]