Emerging nanobiomaterials against bacterial infections in postantibiotic era

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Funding information
Nature Science Foundation of China, Grant/Award Number: 51933009; National Key Research and Development Program of China, Grant/Award Number: 2017YFB0702500

Abstract
Although numerous antibiotics have been developed and applied in clinic, bacterial infections are still serious threats to human health, due to the rapidly growing antibiotic resistance all over the world. The causes of antibiotic resistance include two main aspects: the formation of bacterial biofilms and the self-evolution of bacteria under the antibiotic selection pressure. It is of great significance to develop effective strategies to treat the bacterial infections with serious antibiotic resistance. With excellent performance, such as size effect, specific physicochemical property, easy modification, and so on, nanomaterials exhibit enormous potential as enhancers or therapeutic agents to treat severe drug-resistant bacterial infections. In this review, the underlying causes for the antibiotic resistance are fully summarized and discussed. Subsequently, the promising therapeutic methods by using nanomaterials are provided and discussed to treat bacterial infections with serious antibiotic resistance.

KEYWORDS
antibiotic resistance, antibiotic therapy, nanomaterials, nonantibiotic therapy

1 | INTRODUCTION

The history of human development has always been, to some extent, the history of the continuous struggle against various diseases. Among these diseases, bacterial infection is one of the biggest threats to public health.\(^1\,^2\) Bacterial infection is caused by the pathogenic bacteria on the surface of the organism or inside the organism, which can lead to dysfunction or death of cells, tissues, and organs by producing toxins or other metabolic substances.\(^3\) Numerous diseases with the characteristics of “easy to infect, easy to circulate, difficult to predict, and difficult to control,” including chronic pneumonia, acute bronchitis, meningitis, bacterial pericarditis, bacterial liver abscess, bacterial dysentery, bacterial keratitis, and sepsis, are caused by bacterial infections.\(^4\) In addition, in the preantibiotic era, when antibiotics were not discovered and used, bacterial infections showed extremely high morbidity and mortality.\(^5\) For example, as the first of 39 infectious diseases, the plague caused by \textit{Yersinia pestis} had caused hundreds of millions of people dead in history.\(^5\) Similarly, tuberculosis, which resulted in tuberculosis bacilli, has led to over 200 million deaths to date.\(^6\) Without treatment, cholera caused by \textit{Vibrio cholerae} takes only a few hours from infection to death, resulting in a high fatality rate.\(^7\) In the preantibiotic era, it is beyond doubt that diseases...
caused by bacterial infections are the biggest killers of human health. 8

A variety of antibiotics, as the secondary metabolites produced by certain microorganisms including fungi and actinomycetes, have been widely used for the treatment of bacterial infections since 1920s. 9 In the past few decades, antibiotics have become the first-line drug for treating bacterial infections and greatly reduced the morbidity and mortality, making great contributions to the life extension and rewriting the history of public health. 10 Antibiotics are widely used in clinic for treating various infectious diseases, not only because of their highly effective bactericidal ability but also due to their very low toxicity to healthy mammalian cells. 9,11 The bactericidal mechanisms of antibiotics mainly include changing the bacterial cell membrane permeability, inhibiting the synthesis of bacterial cell walls, restraining bacterial gene replication or transcription, preventing bacterial virulence factors or protein expression synthesis, and so forth. 12 It is the reason why antibiotics are ranked as the greatest discoveries in the field of medicine and health in the 20th century. 13 Up to date, antibiotics still play an irreplaceable role in treating bacterial infections.

However, it is undeniable that the antibiotic resistance is increasingly serious with the abuse of antibiotics. Antibiotic resistance refers to the phenomenon that bacteria are insensitive or even ineffective to antibiotics. 14 For the past few decades, the antibiotic resistance has been becoming increasingly serious and a variety of drug-resistant “superbugs” including Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa are spreading at an alarming rate around the world. 15 Usually, in order to achieve effective therapy of bacterial infections with antibiotic resistance, the dose of antibiotics has increased by several times or even thousands of times, leading to more serious antibiotic resistance. 16 In 2010, the New Delhi metallo-beta-lactamase (NDM-I), which exhibited strong resistance to almost all antibiotics including carbapenem, one of the most effective antibiotics, was found in India and Pakistan, indicating that the antibiotic resistance is coming to extraordinarily serious degree. 2 In order to treat stubborn resistant bacterial infections, polymyxins including polymyxin B and polymyxin E, which were not used clinically for many years due to their obvious nephrotoxicity and neurotoxicity, have to be reintroduced as the last resort. 17 However, regrettably, the resistance to polymyxins has also arisen in clinic. 18 According to the reports from World Health Organization (WHO), the number of deaths from antibiotic resistance worldwide rose from 50 000 in 2010 to 700 000 in 2019, more than the total number of people dying from tetanus, cholera, and measles. 19,20 In addition, it is estimated that the number of deaths caused by antibiotic resistance (10 million/year) will exceed that caused by cancers (8.2 million/year) by 2050. 21,22 At that time, the bacterial infection may become the biggest killer if no new antibiotic or strategy is developed in the intervening years.

Faced with the increasingly serious antibiotic resistance, people had pinned their hopes on the discovery of new antibiotics. 23 Unfortunately, it is regrettable that the speed of the discovery of new antibiotics has lagged far behind that of the increasing bacterial resistance. According to statistics, the number of newly discovered antibiotics has dropped sharply in the past 30 years and there is even a gap of new drugs. 24 In 2013, WHO declared that humans entered the postantibiotic era. 14,18 In 2015, WHO launched a global action plan calling on countries to raise awareness of the problem of antibiotic resistance. 22 In a word, antibiotic resistance has become an extremely severe problem in clinic. With the increasingly serious bacterial resistance, the therapeutic effect of antibiotics on various bacterial infections is becoming weaker and weaker. The problem of bacterial resistance, if not addressed in time, will lead to a return to the preantibiotic era, where a common cold and minor cuts could be fatal. Thus, new strategies are urgently needed to tackle the problem of antibiotic resistance.

With excellent performance, such as size effect, specific physicochemical property, easy modification, and so on, nanomaterials exhibit enormous potential as enhancers or therapeutic agents to treat severe drug-resistant bacterial infections. In this review, we aim to provide an overview of the strategies to overcome the serious crisis of antibiotic resistance and give various facets of emerging methods to remove bacterial infections via advanced nanotechnology. At first, the causes of bacterial resistance are analyzed and discussed, because figuring the reasons for antibiotic resistance out is the foundation to better resolve this problem. Next, we summarize and discuss the promising strategies including the antibiotic therapy and nonantibiotic therapy by using nanomaterials. Here, we will not discuss the antibacterial strategies by employing surfaces or coating, as the antibacterial modes and mechanism of them exhibit great difference compared with that of nanoparticles. We provide the interested readers with excellent research articles and reviews. 25,26 At last, an outlook of potential challenges to treat the bacterial infectious diseases with serious antibiotic resistance is given and discussed.

2 | THE CAUSES OF ANTIBIOTIC RESISTANCE

In the face of the serious problem of antibiotic resistance, it is important to figure out the causes of this problem
carefully. The reasons for the outbreak of bacterial resistance problem mainly contain two aspects: the formation of bacterial biofilms and the self-evolution of bacteria under the antibiotic selection pressure.

2.1 Formation of bacterial biofilms

The formation of biofilm by bacteria is the first major cause of antibiotic resistance. Compared to planktonic bacteria, almost all biofilms exhibit grievous antibiotic resistance. It is reported that biofilm-induced infectious diseases are accounted for more than 80% of clinical infectious diseases. Numerous chronic infectious diseases and refractory infectious diseases, such as diffuse bronchiolitis, periodontitis, osteomyelitis, kidney stones, chronic prostatitis, infective endocarditis, and pulmonary cystic fibrosis, are all closely related to biofilms. According to the reports from American Centers for Disease Control (CDC), biofilms caused 200 million infections in 2018 and nearly 90,000 people died directly or indirectly from biofilm infections in America alone, which resulted in billions of dollars economic losses. Compared with the infections caused by planktonic bacteria, the infections triggered by biofilms show some differences. Antibiotics can effectively kill bacteria on the surface of biofilms, so they usually play great roles in early stage of treatment, whereas they are powerless to kill the bacteria deep inside, resulting in the failure of later treatment. Thus, the resting and attacking period of biofilm infection can constantly transform with each other, which is easy to lead to chronic infection or recurrent attack. Furthermore, the biofilm-mediated immune response of body produces a large number of antibodies to accumulate in the infected sites, resulting in chronic inflammatory response and immune damage. More importantly, the antibiotic resistance of biofilms is 10-1000 times higher than that of planktonic bacteria.

2.1.1 Structure and formation process of biofilms

Biofilms, forming in living tissue such as the lining of the heart or in necrotic tissue, are consist of a large number of extracellular polymeric substances (EPS) and the packaged bacteria. The EPS includes water, fiber, lipid, protein, polysaccharide, lipopolysaccharide, extracellular DNA, and phospholipids. Bacteria are encased in a columnar or mushroom-like extracellular matrix, interspersed with channels and pores for material exchange. The formation process of biofilm is divided into four stages: bacterial adhesion, microcolony formation, biofilm maturation, and bacterial dispersion. At first, the bacteria adhere to the tissue or substrate surface through multiple interactions including hydrophobic action, van der Waals force, and electrostatic attraction, thereby forming the initial adhesion. The adhesion of bacteria on the surface is closely related to the concentration of bacteria, nutrient concentration of environment, temperature, contact time, surface physical or chemical properties of tissue, and pili or flagella on the surface of bacteria.
this period, antibiotic resistance is very weak due to lacking the protective effect of extracellular matrix. After initial adhesion, bacteria will start the expression of certain genes and secretion of EPS. In this stage, with the increasing secretion of extracellular matrix and the increasing number of bacteria, antibiotic resistance is gradually increased. 

With the increasing number of microcolonies, the biofilm would become mature. At this time, the biofilm with a highly organized structure shows great heterogeneity due to the change of the surrounding microenvironment. Once biofilm matures, the protective layer can protect bacteria inside by buffering against changes in the external microenvironment. The structure of biofilm at this stage is complete and the resistance to antibiotic is the strongest. After the biofilm matures, some bacterial clusters or individuals would break away from the matrix and spread to other parts. Then they colonize again, forming new biofilms. At this stage, the bacteria in biofilm are spreading ceaselessly, which aggravates the infections.

### 2.1.2 Causes of biofilm resistance to antibiotics

The complex structural composition and formation process endue biofilm complex microenvironment, which changes the growth and metabolism status of bacteria in biofilm. Biofilm is difficult to be eradicated and the residual strains in deep biofilm can reproduce in large number to form new biofilms. The main reasons for biofilm resistance to antibiotic include the following aspects.

#### The change of microenvironment

Compared with the microenvironment where planktonic bacteria live, the biofilm microenvironment is significantly different, showing noteworthy heterogeneity, for example, biofilm exhibiting obvious nutrient gradient and oxygen gradient. The oxygen diffusion into biofilm is much less than oxygen consumption by bacteria, thus the biofilm is in a hypoxic state and the degree of hypoxia increases with biofilm depth increasing. It was reported that in a *P. aeruginosa* biofilm with a thickness of 80 µm, it was hypoxic in the upper 30 µm and the hypoxia degree increased with the increase of depth, whereas in the lower 50 µm, the biofilm was basically in an anaerobic state. It has been demonstrated that biofilm hypoxia significantly reduces the efficacy of many antibiotics, which contributes to biofilm resistance. For example, in the hypoxic state, the bactericidal efficacy of aminoglycoside antibiotics is significantly lower than its efficacy in the normal oxygen environment. In addition, the hypoxia induces anaerobic degradation of biofilm, resulting in the production and accumulation of abundant acidic metabolites. Therefore, the concentration of hydrogen ions in biofilm can increase by an order of magnitude or even higher, leading to lower pH of biofilm compared with that of normal tissues. Most antibiotics show excellent bactericidal effects in neutral conditions. However, they can be deactivated by acid degradation or acid passivation in acidic microenvironment, leading to greatly reduced bacterial capacity. Moreover, in the hypoxic and acidic microenvironment, bacteria would start the self-protection process and secrete a large amount of reductive substances, such as glutathione (GSH) and coenzyme A, resulting in a highly reductive state of the entire biofilm, which would greatly reduce the activity of antibiotics.

#### The shielding and impedance of EPS to antibiotic

The EPS of biofilm contain a large number of alginate and polysaccharide substances with very large fluid viscosity, thereby showing strong physical impedance to antibiotics. Alginate can absorb part of antibiotics through van der Waals force, hydrogen bond, and other interactions. The anionic substances in EPS also exhibit great inhibiting effect to cationic antibiotics through electrostatic interaction and chelation. In addition, various enzymes in EPS, such as hydrolase and catalase, can degrade and inactivate antibiotics. The EPS of biofilm contain a large number of alginate and polysaccharide substances with very large fluid viscosity, thereby showing strong physical impedance to antibiotics. Alginate can absorb part of antibiotics through van der Waals force, hydrogen bond, and other interactions. The anionic substances in EPS also exhibit great inhibiting effect to cationic antibiotics through electrostatic interaction and chelation. In addition, various enzymes in EPS, such as hydrolase and catalase, can degrade and inactivate antibiotics. The EPS of biofilm contain a large number of alginate and polysaccharide substances with very large fluid viscosity, thereby showing strong physical impedance to antibiotics. Alginate can absorb part of antibiotics through van der Waals force, hydrogen bond, and other interactions. The anionic substances in EPS also exhibit great inhibiting effect to cationic antibiotics through electrostatic interaction and chelation. In addition, various enzymes in EPS, such as hydrolase and catalase, can degrade and inactivate antibiotics.

#### The low metabolic activity or dormancy of bacteria in biofilm

The morphology, metabolism, and physical and chemical characteristics of bacteria in biofilm are significantly different from those of planktonic bacteria. Even in the same biofilm, bacteria also have extensive heterogeneity. For instance, the metabolic activity of bacteria at different biofilm locations are significantly different. Biofilms are divided into surface layer, junction layer, conditional layer, and matrix layer. In the surface layer of biofilm, bacteria are easy to obtain oxygen or nutrients and the metabolites are easy to be excreted. Therefore, these bacteria show similar metabolism with planktonic bacteria with high activity and weak resistance to antibiotics. Bacteria in the middle and bottom layer of biofilm are closely wrapped in the EPS. Thus, bacteria are in very low metabolic activities or dormant state, showing highly resistance to antibiotics.
FIGURE 2 Quorum sensing in *Pseudomonas aeruginosa* biofilms accelerates cell growth and new biofilm development

Because most antibiotics can only target and kill bacteria in normal metabolism or rapid growth state, bacteria in low activity or dormant bacteria in the middle and bottom layers of the biofilm continually increase the biofilm resistance to antibiotics.51

**Quorum sensing of biofilm**

It has been demonstrated that quorum sensing (QS) of biofilm is another major reason for antibiotic resistance.52 Bacteria in biofilm can secrete plenty of inducers to discern the quantitative changes of bacteria and the concentration changes of oxygen and nutrient. When the density of bacteria reaches a certain threshold or the oxygen and nutrient are insufficient, bacteria will start the expression of some genes, secretion of signal molecule, and regulation of population density. The regulation system is known as QS system.52 The regulatory effect of QS system on antibiotic resistance is mainly demonstrated in two aspects.35,53 First, the QS promotes the secretion of exopolysaccharides, alginate, and other substances. In the meanwhile, it activates bacterial aggregation through signal molecules, regulating the formation and consolidation of biofilm (Figure 2), furtherly improving antibiotic resistance.54 Second, the QS can improve antibiotic resistance by regulating the efflux function of the bacterial efflux pump.

**The enhancement of bacteria efflux pump**

The bacterial efflux pump, showing excellent ability to exclude antibiotics out from bacteria, is composed of three parts from the inside to the outside, which are extracellular proteins, fusion proteins, and extracellular channel proteins. With the participation of energy, these three proteins can work together to remove foreign substances such as antibiotics from bacteria.55 Compared with planktonic bacteria, in order to adapt to the complex microenvironment and improve their viability, bacteria in biofilm would significantly enhance their efflux pump function, ultimately leading to serious antibiotic resistance.

### 2.2 Self-evolution of bacteria under antibiotic selection pressure

Apart from the formation of bacterial biofilms, the self-evolution of bacteria under antibiotic selection pressure is another important reason. Antibiotic resistance of planktonic bacteria is split into natural resistance and acquired resistance according to the method of acquisition.48 Bacteria in nature, due to the special chemical composition and structure, are determined to possess the inherent drug resistance, named as natural resistance.56 The natural antibiotic resistance is caused by several factors.48,56,57 For example, some bacteria producing antibiotic hydrolase, some bacteria changing cell walls and cell membrane permeability, some bacteria possessing strong efflux ability, and some bacteria changing the metabolic pathways.

It is known that the bactericidal process of antibiotics is a process of natural selection between bacteria and antibiotics. For long-term use of one kind of antibiotics, most of sensitive strains are wiped out, whereas drug-resistant strains can be selected to survive, leading to the rising prevalence and accumulation of resistance to this antibiotic.57 It is noteworthy that the acquired antibiotic resistance can be inherited by transferring drug-resistant genes to chromosomes, ultimately becoming inherent resistance. In the preantibiotic era, the antibiotic resistance was basic natural drug resistance and the proportion of strains with natural antibiotic resistance was very low.59 In recent decades, bacteria have continuously evolved and mutated under the antibiotic selection pressure, resulting in more drug-resistant genes screened and preserved. When bacteria become genetically resistant to an antibiotic, the bactericidal activity of this antibiotic is greatly reduced or even disappeared.58 For example, at the beginning, most *P. aeruginosa* were sensitive to ceftazidime, but with the continuous use of this antibiotic, the surviving bacteria can still survive even under very high concentration of antibiotic.59 To make matters worse, these bacteria with high antibiotic resistance can also gather to form biofilms, leading to the further strengthened drug resistance. At present, such biofilms basically face the difficult situation of no antibiotic available.

It is obvious that the drug resistance caused by self-evolution and mutation of bacteria under the long-term selection pressure of antibiotic is an inevitable problem in the era of antibiotic.55 It is worth noting that irrational use of antibiotic, that is, excessive use of antibiotic in excess of range, dosage, and time, can greatly accelerate the formation and accumulation of the acquired antibiotic resistance. The abuse of antibiotics is one of the main culprits of the growing drug resistance. Irrational use of antibiotic, which has led to the emergence of numerous drug-resistant bacteria, such as methicillin-resistant...
Staphylococcus aureus (MRSA), vancomycin-resistant Staphylococcus aureus (VRSA), and multidrug-resistant P. aeruginosa, is widespread in the world in clinic. In addition, there are also a large number of abuse of antibiotic in agriculture, poultry, and animal husbandry industries. The resulting problem of drug resistance eventually comes to humans through the food chain.

3 | NANOMATERIALS

Nanomaterials are defined as possessing at least one dimension between 1 and 100 nm in three dimensions. In recent years, the rapid development of nanotechnology has brought new hope for the application of nanomaterials in the biomedical field. Compared with traditional large-scale materials, nanomaterials have many incomparable advantages due to their special size, extremely high specific surface area, and unique optical, mechanical, thermal, electromagnetic, and mechanical properties. In addition, nanomaterials can be modified with various functional groups. The modified nanomaterials can significantly improve their behaviors in organisms, such as improving the stability during blood circulation, enhancing the uptake of tissues and cells. After decades of research, nanobiomaterials have shown great potential in diagnosis and treatment of many major diseases such as cancer, refractory bacterial infection, diabetes, and viral infection. With many excellent properties, nanomaterials will have a broad application in health fields.

3.1 | Nanomaterials for changing the microenvironment or structure of diseased tissues

In general, the microenvironment of diseased tissues is significantly different from that of healthy ones. For example, hypoxia, low pH, and high GSH concentration are widespread in tumor tissues and bacteria-infected tissues. In addition, the structure and composition of diseased tissues also show great difference with healthy tissues. For instance, there are dense stroma in pancreatic cancer tissues and abundant extracellular DNA (eDNA) in bacterial biofilms. In many cases, the markedly different microenvironment and structure of diseased tissues are the important reasons for drug failure. Therefore, a change of microenvironment or structure of diseased tissues may have positive effects in drug therapy. As mentioned above, nanomaterials have many excellent properties, among which their small size gives nanomaterials good vascular and tissue penetration. After infiltration into the tissues, the unique properties of the nanomaterials or the drugs they carry can bring great changes to the microenvironment. For example, bismuth selenide nanoparticles loaded with perfluorohexane can deliver oxygen to diseased tissues, thus relieving their hypoxia. Micelles containing nitric oxide donors can deliver nitric oxide to diseased tissues, enhancing the relaxation of vascular smooth muscle cells, decreasing the concentration of overexpressed GSH. Liposomes loaded with S-nitroso-N-acetylpenicillamine can be used to delivery nitric oxide to restrain the production of compact extracellular stroma, by restraining the TGF-β1 expression and inhibiting the transduction of downstream signal. Mesoporous silica nanoparticles can act as supporting scaffolds to encapsulate deoxyribonuclease I (DNase I) and delivery DNase I into biofilms. DNase I can disintegrate eDNA of biofilm EPS, ultimately changing the structure of biofilm. Once the microenvironment or the structure of diseased tissues was changed, the pathogenic factor might be weakened or removed, showing great benefits for treating the bacterial infections or cancers.

3.2 | Nanomaterials for disease treatment

In recent years, a good deal of nanomaterials have been researched to treat various diseases due to their special physical and chemical properties. For example, silver, copper, and zinc oxide nanoparticles have excellent bactericidal effect and can be used as nanofungicides. Micelles, liposomes, and other organic nanomaterials have excellent drug encapsulation capacity, which can be employed for encapsulating drugs, improving the biological distribution of drugs, enhancing the local therapeutic concentration of drugs, and reducing the toxic of drugs. Magnetic nanomaterials can not only be used as diagnostic agents, but also be used for targeted drug delivery. Gold nanoparticles, graphene nanomaterials, and molybdenum disulfide nanomaterials have good photothermal transformation capacity, which can be used as nano heat source for photothermal therapy. With excellent performance of generating reactive oxygen species (ROS), black phosphorus nanosheets can be employed for photodynamic therapy under laser irradiation.

4 | THERAPEUTIC METHODS OF BACTERIAL INFECTIONS WITH SERIOUS ANTIBIOTIC RESISTANCE

4.1 | Antibiotic therapy

The problem of antibiotic resistance is not achieved overnight, but accumulated over a certain period of time.
It is noteworthy that in this process, the abuse of antibiotics drastically accelerates the accumulation of resistance. At the same time, it is undeniable that antibiotics are still effective drugs for the treatment of most bacterial infections at present. Therefore, the proper use of antibiotic, especially rational control and decrease of antibiotic doses, is of great significance to reduce the harm of drug resistance and delay the development of antibiotic resistance.

As previously mentioned, the antibiotic resistance is closely related to these factors, such as the shielding or impedance of EPS to antibiotic, the enhancement of QS, the structural change of planktonic bacteria, the decrease of bacterial metabolic activity, and so on. Once the aforementioned structure or microenvironment of biofilms and the structure of planktonic bacteria are changed, these antibiotic resistances may be greatly reduced or even disappear.

4.1.1 Enhanced antibiotic therapy assisted by increasing drug penetration into biofilms

The shield and impedance of antibiotic penetrating into biofilm by EPS is one of the important reasons for greatly decreased bacterial efficacy of antibiotics. Therefore, enhancing the penetration of antibiotics into biofilm shows great potentials to improve the bacterial efficacy of drugs. Although exhibiting excellent antibacterial ability, plenty of hydrophobic antibacterial agents are not applicable to practical application due to their poor solubility in blood stream. Polymeric nanoparticles can effectively solve this problem by packaging the hydrophobic antibacterial agents into their interior. Rotello et al developed a GSH-sensitive cross-linked poly(oxyanorborneneimide) nanoparticles, into which carvacrol with excellent antibacterial ability was packaged. The nanoparticles showed great long-term stability in aqueous solution, whereas the nanoparticles could degrade and release the carvacrol in the bacterial infected sites because the GSH promoted the disulfides in the nanoparticles breaking. Both Gram-positive and Gram-negative bacteria containing the drug-resistant strains could be effectively killed by the cavaacrol. In addition to the GSH-sensitive polymeric nanoparticles, Rotello et al also reported the pH-responsive polymeric nanocarriers acting as the drug delivering system. They demonstrated that the pH-responsive imine bonds were very stable in the physiological pH, whereas in the acidic bacterial infected sites, the nanoparticles showed rapid drug-releasing behavior and killed the bacteria effectively. Shi et al developed a kind of polymeric micelles with mixed shells, composed of pH-responsive poly(β-amino ester) (PAE) and hydrophilic polyethylene glycol (PEG). In normal tissues (pH 7.4), the PEG shell was exposed, whereas the PAE block was collapsed on the micelle; thus, these micelles were biologically invisible and showed a good long-time circulation. In acidic biofilm (pH ∼5.0), the PAE block became hydrophilic and possessed abundant positive charges, due to the protonation of imino group. The positively charged surface of micelles vastly promoted the penetration of antibiotics into biofilms and adhered to the negatively charged bacteria. Upon penetrating into biofilms, the micelles could be degraded by the bacterial lipases and released the drug to kill bacteria. They demonstrated that the micelles with positively charged surface exhibited better penetration ability into biofilms compared with negatively charged micelles. In addition, to achieve the efficient penetration and diffusion of antibiotics in biofilm, Shi and his colleagues reported another drug delivery nanocarrier, which was fabricated by packing chitosan nanoparticles with poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC). These nanocarriers showed low EPS adsorption because the PMPC could combine water molecules to yield a specific surface for impeding nonspecific adsorption of protein. These nanocarriers exhibited enhanced penetration ability into biofilms and valid target to the negatively charged bacteria, because the chitosan (pKₐ ∼6.5) could be protonated in acidic biofilm (pH ∼5.0). Additionally, the hydrophobic drugs were released with the disintegration of chitosan core. With the enhanced penetration of drugs into biofilms, the bactericidal efficacy was vastly improved. In order to better transfer antibiotic to bacterial infection sites, Zhang et al reported a directional transport system that the nanoparticles could respond to the bacteria directly rather the bacterial microenvironment. In their system, nanoparticles could stop the antibacterial agents inside from leakage in the circulation process, but leading to the rapid release of antibacterial agents once the nanoparticles bind to the surface of bacteria, achieving the great delivery of antibacterial agents.

4.1.2 Enhanced antibiotic therapy assisted by physical destroy of EPS

Apart from endowing antibiotics with excellent penetration ability into biofilms, disturbing or destroying the EPS of biofilm can also improve the therapeutic efficacy of antibiotics. It was reported that the transportation efficiency of gentamicin into P. aeruginosa biofilm could be greatly improved after the ultrasound therapy. Ultimately, with the penetration amount increasing, the bactericidal effect of gentamicin was remarkably enhanced. Chakravortty and his co-workers demonstrated that the shock waves could exhibit great damage capability to
biofilm construction of *S. aureus* and *P. aeruginosa*, thus reducing their resistance to ciprofloxacin. Braeckmans et al reported a strategy by using the gold nanoparticles (AuNPs) and laser treatment to locally destroy the integrity of biofilm, which could greatly promote antibiotic to penetrate into bottom of biofilm and improve their therapeutic efficiency. When the laser with high-intensity and short pulse (≤10 ns) irradiated to the biofilm that had been incubated with AuNPs suspension ahead of time, the temperature of AuNPs could increase to several hundreds of degree. The high temperature made the surrounding water evaporate and generate water vapor nanobubbles, promoting tobramycin to reach the bacteria more easily even the bacteria in the deep layers of biofilm, ultimately improving the therapeutic efficacy of tobramycin. Due to the side effect of shock waves, ultrasound and vapor nanobubbles with high temperature are still uncertain, such as bleeding and tissue damage. Therefore, it is of great significance to develop some methods that can refine the physical destructions of biofilm only in infectious sites rather than the whole tissues.

### 4.1.3 Enhanced antibiotic therapy assisted by enzymatic degradation of EPS

Another effective strategy to destroy the integrity of biofilm is enzymatic degradation of EPS. As an important component of biofilm EPS, alginate, which can promote the formation of *P. aeruginosa* biofilm, has been demonstrated to be closely related to the antibiotic resistance. To address this problem, Zhang et al developed a kind of porous silica nanocomposites that could deliver alginate lyase and ceftazidime to eradicate *P. aeruginosa* biofilm in infected lungs. In the acidic biofilm microenvironment, the catalytic activity of the alginate lyase was greatly enhanced, promoting the degradation of alginate. At the same time, the nanocomposites could exhibit rapid release of ceftazidime to kill bacteria (Figure 3). eDNA, as the longest molecule in EPS, can not only serve as the bridge among bacteria, but also form the mature network with other components of EPS. It was reported that destroying eDNA by DNase could disintegrate biofilm and improve the sensitivity of antibiotics. Castro et al developed a kind of...
lipid nanoparticles for encapsulation of levofloxacin and DNase. While penetrating into the biofilm, the DNase could act as mucolytic enzyme to degrade the eDNA, thereby decomposing the EPS. The bactericidal efficacy of levofloxacin was dramatically improved after the EPS was dismembered. Nagarsenker et al demonstrated that the liposomes loaded with serratiopeptidase could distinctively disrupt the EPS of *S. aureus* biofilm and enhance the bactericidal efficacy of levofloxacin. Moreover, they also observed great probability to employ the dry powder of serratiopeptidase and levofloxacin liposomes to treat the biofilm infection in lungs by inhalational therapy. However, due to the lack of long-term activity and difficulty in recovery, the cost of natural enzymes is usually very high. Moreover, natural enzymes also show low operational stability and the high environmental sensitivity in organisms. There is no doubt that the above shortcomings immensely limit their practical application in biofilm therapy. Enlightened by the mechanism of natural enzymes in decomposing EPS and the molecular structures of natural enzymes, plenty of efforts have been put into constructing enzyme mimics that possess high catalytic ability and stability. For example, Qu et al reported that the DNase-mimetic artificial enzyme, which was obtained by restricting inactive AuNPs and multiple cerium complexes onto the surface of colloidal magnetic Fe₃O₄/SiO₂ core/shell nanoparticles, not only could dramatically facilitate antibiotics to effectively kill biofilm-encased bacteria by decomposing EPS, but also showed easier recoverability and better operational stability.

### 4.1.4 Enhanced antibiotic therapy assisted by suppressing QS

QS has been demonstrated to play an important role in the formation process of biofilm and show close relationship with the biofilm resistance to antibiotics. In recent years, quorum sensing inhibitors (QSI), such as cinnamaldehyde, hamamelitannin, and baicalin hydrate, have been widely studied to inhibit the QS, further restraining the formation of biofilm or promoting the mature biofilm dispersing. Coenye et al observed that both baicalin hydrate targeting to acylhomoserine lactone-based QS system in *P. aeruginosa* biofilm and hamamelitannin targeting to the peptide-based system in *S. aureus* biofilm exhibited excellent structure damage to biofilms. After treated with QSI, both the sensitivity of tobramycin to *P. aeruginosa* biofilm and the sensitivity of vancomycin to *S. aureus* biofilm were greatly improved, demonstrating the QSI could remarkably enhance bactericidal effect of antibiotics. It is noteworthy that on direct injection of QSI into vein without any modification, not only the efficiency of QSI would greatly be decreased due to the passivation by compounds in the circulation system, but also the QSI might lead to some severe side effects including the proteolytic degradation of host-associated proteins. Therefore, it is necessary to deliver QSI in a carrier and maintain the effective concentrations of QSI in biofilm infectious sites rather than the whole body to bring about an outstanding destruction of QS of biofilms when developing the practical anti-QS drugs. To address this issue, Lee et al reported a poly(lactide-coglycolide) particle system that could act as a good carrier of furanone C-30 (a kind of QSI) for the long-term release of QSI to better destroy biofilm. If antibiotic was added, a higher therapeutic efficacy of the combination treatment would be obtained when comparing with the antibiotic therapy alone. Qu et al developed the hollow carbon nitride spheres that loaded luteolin (L) as QSI and ampicillin. Luteolin showed enhanced sensitization effect of antibiotics in biofilm treatment. The mechanism of QSI enhancing the bactericidal effect of antibiotics mainly includes two aspects. On the one hand, QSI can effectively inhibit the formation and growth of biofilm or destroy the mature biofilm, further increasing the sensitivity of antibiotics to bacteria. On the other hand, the bacterial virulence in biofilm could be greatly attenuated by QSI, assisting antibiotics to kill bacteria. Moreover, this approach also shows a drawback that is the QSI exhibits high specificity. Thus, the therapeutic method can only be used in some certain biofilm infections rather than a wide range of bacterial infections, for example, it becomes troublesome in the treatment of multispecies biofilm infections in vivo.

### 4.1.5 Enhanced antibiotic therapy assisted by destroying bacterial specific structure

The antibiotic resistance of some planktonic bacteria, such as MRSA, is due partly to the change of some specific structure of bacteria. For example, compared with *S. aureus*, vast resistance exhibited by MRSA to methicillin was attributed to the lower membrane permeability, the production of β-lactamase, and the disappearance of antibiotic targets. Therefore, destroying some specific structure of bacteria can enhance the therapeutic efficacy of antibiotics. Hu et al designed a kind of micelle that was polymerized by triclosan prodrug monomer and hydrophilic poly(N,N-dimethylaminoethyl methacrylate) (PDMAEMA). The triclosan prodrug acted as the hydrophobic core and the PDMAEMA block served as the hydrophilic shell with quaternization potency in acidic bacterial infectious sites to improve the charge density. The abundant positive charges of micelles could lead to severe membrane damage of bacteria and out-diffusion...
of cytosolic milieu across the membrane. When getting into the bacteria, the release of triclosan could effectively inhibit the biosynthesis of fatty acid, showing enhanced bactericidal effect compared with triclosan therapy alone.

### 4.1.6 Enhanced antibiotic therapy assisted by delivering antibiotic cargo intracellularly

Intracellular infections, exhibiting serious threats to human health, are extremely difficult to treat due to the capacity of bacteria hiding within macrophages. It is a great challenge to deliver antibiotic intracellularly. Metal-organic framework (MOF)-based nanomaterials with outstanding (a) ability of loading various drugs, (b) biocompatibility and precise control of particle size, and (c) facile surface chemistry allowing conjugation of numerous functionalities show good potential to deliver the antibiotic intracellularly, which is a promising methodology to enhance the treatment of intracellular infections. McBride et al. proposed a MOF-based system as a valid slow-release therapeutic carrier for treating intracellular infections.\textsuperscript{101} The ceftazidime was encapsulated in ZIF-8 nanoparticles as a potential therapeutic agent. Ceftazidime@ZIF-8 nanoparticles exhibited excellent cell penetration ability and bactericidal ability intracellularly, indicating this strategy is a promising methodology to enhance the treatment of intracellular infections.

### 4.2 Nonantibiotic therapy

Some planktonic bacteria, such as VRSA, have already showed up invalid antibiotic therapy due to the super antibiotic resistance. If these bacteria with strong antibiotic resistance form biofilms, the antibiotic resistance will be more serious. In order to treat the infections with strong antibiotic resistance, the bactericidal strategy of the combination of destroying bacterial or biofilm structure and antibiotic is feeble or invalid. Therefore, developing and reserving some novel methods different from antibiotic therapy will not only be beneficial to solve the drug resistance problem at present, but also show much strategic significance to further control the problem of antibiotic resistance in the future.

#### 4.2.1 Phototherapy

Among nonantibiotic therapies, phototherapy is one of important therapeutic methods besides surgery and radiotherapy. Compared with the drug resistance caused by chemical therapy and the trauma caused by surgical treatment, phototherapy based on nanomaterials shows great potentials as noninvasive treatment methods. As representatives of phototherapy, photothermal therapy and photodynamic therapy have been widely studied.

**Photothermal therapy**

Photothermal therapy is a therapeutic method that employs photothermal conversion materials to convert light energy into heat energy under light irradiation to kill bacteria by high temperature.\textsuperscript{63,102} Compared with ultraviolet or visible light, near-infrared (NIR; 700-1300 nm) light has deeper tissue penetrating ability, thus it is often employed as the preferred light for photothermal therapy. Photothermal conversion materials usually have the characteristics of high absorption intensity, high photothermal conversion rate, and good photothermal stability. Up to now, the commonly used photothermal conversion materials mainly include small molecular organic materials, organic nanomaterials, and inorganic nanomaterials.\textsuperscript{103} Although these photothermal conversion materials have excellent photothermal conversion efficiency, there are some differences among them. Small-molecule organic materials include indocyanine green, IR780, and so on, which have the advantages of low toxicity, easy loading, and easy metabolism, but poor water solubility and poor photostability such as photobleaching.\textsuperscript{104} Organic nanomaterials include conjugated polymers such as polypyrrole, polyaniline, and polydopamine. Compared with small-molecule organic materials, such photothermal materials have the advantages of good biocompatibility, high photothermal stability, and easy postmodification, but the preparation process of such materials is often complex.\textsuperscript{105} The inorganic nanomaterials contain gold nanomaterials, carbon nanomaterials, and excessive metal sulfide nanomaterials. Compared with small-molecule organic materials and organic nanomaterials, inorganic nanomaterials have advantages of good photothermal stability, easy modification, and simple preparation, but their metabolism needs further investigation.\textsuperscript{79,106}

One of major challenges in photothermal therapy is to restrain the spatial distribution of photothermal conversion materials to ensure the heat in infected sites only, because the nonlocalized heat can greatly damage healthy tissues. To address this issue, we reported a kind of bacteria-targeted polydopamine nanoparticles (PDA-PEG-Van), fabricated by embellishing thiol-poly(ethylene glycol) (mPEG-SH) and vancomycin (Van) molecules based on Schiff base reaction and Michael reaction onto the surface of polydopamine nanoparticles.\textsuperscript{107} Due to the specific binding with terminal D-Ala-D-Ala moieties of cell wall, PDA-PEG-Van nanoparticles could adhere to the surface of MRSA and kill them effectively under NIR light even at
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![Figure 4](image)

**FIGURE 4** (A) Schematic illustration of the pH responsiveness of gold nanoparticles. (B) AuNP-N-S can disperse stably in methicillin-resistant *Staphylococcus aureus* (MRSA) biofilm and healthy tissues, showing no bactericidal effect under near-infrared (NIR) light irradiation. (C) AuNP-N-C can aggregate in MRSA biofilm, exhibiting good bactericidal ability under NIR light irradiation without damage to healthy tissues.

Mild temperature. Sung et al. reported a kind of injectable polymer solution, which was composed of a chitosan derivative including self-doped polyaniline side chains. This polymer could self-assemble to form micelles in an aqueous environment and shift to colloidal gels in situ at acidic pH (6.0-6.6). The micelle could generate much heat under NIR light irradiation, leading to the thermal ablation of bacteria in acidic infected sites, whereas in healthy tissues where no micelles were distributed, the temperature was normal, leaving negligible damage. Moreover, we reported a surface-adaptive mixed charged zwitterionic gold nanoparticle (AuNP-N-C) to restrain the heat distribution only in biofilm infectious sites for photothermal therapy (Figure 4). AuNP-N-C was prepared by modifying the gold nanoparticles with mixed self-assembled monolayers that was composed of pH-responsive mixed charged ligands. In healthy tissues, the nanoparticles were dispersed, showing no photothermal effect under NIR light irradiation, thus resulting in no damage to healthy tissues, whereas in acidic biofilm-infected sites, the nanoparticles could aggregate rapidly and generate heat under NIR light irradiation, leading to strong bactericidal effect. As is discussed above, the photothermal therapy shows a lot of excitement and optimism, in order to put it in the clinical application, more preclinical studies, such as the minimizing the immune response of nanoparticles and the efficient clearance methods of nanoparticles, should be further studied.

**Photodynamic therapy**

Photodynamic therapy has three important elements: photosensitizers, light, and oxygen. Under the irradiation of light with specific wavelengths, the photosensitizers can absorb light energy and catalyze oxygen to produce singlet
Metal nanoparticles have recently been widely studied for the treatment of bacterial infections due to their unique optical, magnetic, and electrochemical properties and the bactericidal function of some metals themselves. Among them, silver nanoparticle is a typical representative. The bactericidal mechanism of silver nanoparticle mainly includes the following aspects. Silver nanoparticles interact with peptidoglycan, a main component of Gram-negative bacteria cell wall, to create small holes on the cell walls and pass through. Meanwhile, the positively charged silver nanoparticle can combine with the cell membranes with negative charge to interfere with the mobility and permeability of membranes. Silver nanoparticles can also enter the cytoplasm and directly attack the organelles. At the same time, they can inactivate the enzymes and destroy the metabolism of bacterial cells. In addition, the silver nanoparticle can attack the DNA in bacteria, depriving their replication and protein transcription.

With excellent bactericidal ability, silver nanoparticles show great potential to act as effective antibacterial agent. Because silver nanoparticles can react with some salts and sulfur-containing proteins in bloodstream, the aggregation of silver nanoparticles is a major challenge that restricts their clinical application. Apart from killing bacterial cells, silver nanoparticles can also kill normal mammalian cells and damage healthy tissues; hence, the cytotoxicity of sliver nanoparticles is often a great concern for clinical applications. To address these issues, Du et al developed a strategy by employing the biodegradable poly(3-caprolactone)-block-poly(acrylic acid) diblock copolymer as vesicles to pack the silver nanoparticles. The Ag⁺ ions could be absorbed into the carboxyl groups in the poly(acrylic acid) coronas because of the electrostatic interaction. When getting into the bacterial infectious sites with abundant lipase, the poly(3-caprolactone) would be effectively degraded and the silver nanoparticles would be released to kill bacteria. In the presence of lipase, the polymer vesicles could be degraded into debris and ultimately metabolized by organisms. Qu et al reported a kind of surface adaptive antimicrobial nanoparticles for sustained release of silver ions. Silver nanoparticles were infused into the MOF nanostructures (PCN-224-Ag) and the PCN-224-Ag nanoparticles were further modified with negatively charged hyaluronic acid (PCN-224-Ag-HA). The PCN-224-Ag-HA nanoparticles exhibited very low toxicity
to mammal cells due to the excellent protection effect of HA on the surface of nanoparticles, whereas HA would be degraded by the hyaluronidase in bacterial infectious sites, leading to the release of silver nanoparticles. The positively charged PCN-224-Ag$^{+}$ nanoparticles could quickly bind to the negatively charged bacterial cell surface and kill them effectively.

Apart from silver nanoparticles, other metal nanoparticles, including copper, zinc oxide, and titanium dioxide nanoparticles, can also serve as effective antibacterial agents. The mechanisms of these metal nanoparticles include denaturation of proteins by interacting with sulphydryl groups, generation of ROS, binding the carboxyl groups on the cell membrane, disturbing the DNA structures, and so on.

### 4.2.3 Polymeric nanoparticles as antibacterial agents

Polymeric nanoparticles include both natural polymeric nanoparticles such as nanoparticles formed by antimicrobial peptide and synthetic polymeric nanoparticles such as nanoparticles fabricated by polyhydroxyalkanoates, polylactic acid, polycaprolactone (PCL), poly-D-L-glycolide, and polycyanoacrylate. Polymeric nanoparticles show tremendous potentials for antibacterial application due to their incomparable properties. For instance, polymeric nanoparticles with a narrow size distribution can be easily obtained by controlled polymerization process. The nanoparticles properties can be precisely tailored by proper choice of polymer structure and lengths. Moreover, the functional groups on the nanoparticles can be acquired by chemical modification, for example, polymeric nanoparticles can be modified with PEG to enhance the blood circulation capacity. More importantly, polymeric nanoparticles are less sensitive to development of antibiotic resistance by bacteria.

Numerous polymeric nanoparticles can directly serve as antibacterial agents. Yang et al reported a range of core-shell nanoparticles that were fabricated by the self-assembly of amphiphilic peptides (CG3R6TAT). The peptide consists of hydrophilic penetrating peptide for improving the membrane penetration ability, arginine residues for increasing the positive charges to enhance the membrane disturbing, and cholesterol for providing the hydrophobic moieties to drive the self-assembly and enhance the membrane permeability of the micelles. The nanoparticles showed excellent bactericidal ability against *S. aureus* infection in mice. In addition, the nanoparticles could penetrate the blood-brain barrier and exhibit great bacteriostatic action in *S. aureus*-infected brains of rabbits. Qiao et al developed star-shaped peptide polymer nanoparticles, which were composed of lysine and valine residues. These star nanoparticles could be infinitely diluted due to their stable unimolecular architectures. It demonstrated that the star nanoparticles not only exhibited superior antibacterial activity against
various Gram-negative bacteria, but also displayed selectivity toward pathogens over mammalian cells. More importantly, these nanoparticles could also effectively kill colistin-resistant and multidrug-resistant pathogens. The antimicrobial mechanism was multimodal, including disruption of the integrity of bacterial outer membrane and cytoplasmic membrane. It was reported that the polymeric nanoparticles with cationic charge and hydrophobic structures, such as poly-norbornenes, polyacrylates, and polycarbonates, could exhibit outstanding bactericidal ability because they have the similar structure as antimicrobial peptides. Cai et al developed a micelle fabricated by quaternized β-chitin derivatives via a “green” route in an aqueous KOH/urea solution. In their research, the cationic micelles showed remarkable antibacterial ability against S. aureus, E. coli, and C. albicans with the minimum inhibitory concentrations (MIC) of 12, 8, and 60 µg/mL, respectively. More interestingly, the antibacterial activity of cationic polymeric nanoparticles could be regulated by changing the hydrophobic moieties. Rotello et al prepared a series of quaternary ammonium poly(oxnorborneneimides) that had various lengths of hydrophobic moieties. These polymers could form nanoparticles with the size of 10-15 nm in the aqueous solution. In this study, it was demonstrated that the nanoparticles with longer hydrophobic alkyl chains, which connected the polymer backbone with cationic headgroup, exhibited better bactericidal ability to planktonic bacteria. Furthermore, these cationic polymeric nanoparticles could also show excellent biofilm penetration ability and eradicate the mature biofilm. Although cationic polymeric nanoparticles exhibit excellent bactericidal ability, they are generally highly positively charged, resulting in obvious side effects including hemolysis and cytotoxicity to healthy mammalian cells. To solve this issue, Shi et al proposed adaptive biomaterials as novel antibacterial agents. According to variations in the surrounding microenvironment, adaptive biomaterials could adjust their physiochemical properties to adapt themselves to the surrounding microenvironment to enhance their biological functions. Adaptive nanoparticles could effectively deliver antimicrobials into biofilms, thereby enhancing the efficacy of antimicrobial agents and decreasing the dose of antimicrobial agents. Moreover, Du et al reported a kind of antibacterial nanosheet that was self-assembled by hyperbranched polymer grafting with multifunctional antibacterial peptide. This nanosheet exhibited highly effective antibacterial activity against both Gram-positive and Gram-negative bacteria by a “wrapping and penetrating” antibacterial mechanism, but showed very low cytotoxicity because the positive charge of nanosheet was very weak (+6.1 mV). Wang et al designed a gelatinase responsive nanoparticle fabricated by polymer-peptide conjugates composed of chitosan, antimicrobial peptide, and poly(ethylene glycol)-tethered enzyme-cleavable peptide (CPC-1). They observed that the nanoparticles with PEGylated coronas exhibited excellent circulation stability and low toxicity in healthy tissues. The PEG layer of the nanoparticles would be peeled off by the overexpressed gelatinase in the bacterial infectious sites, leading to the destruction of hydrophobic/hydrophilic balance that facilitated the reorganization of nanoparticles into nanofibers. In the circumstances, the nanofiber exposed α-helical structures, resulting in the electrostatic interactions with bacterial membranes to kill bacteria. In addition, to reduce the toxicity of quaternary ammonium moieties to healthy mammalian cells, Du et al developed an antimicrobial polymeric vesicle that did not contain quaternary ammonium moieties. The vesicle was self-assembled by the thermoresponsive diblock copolymer (PMEO₂MA-b-PTA). Poly[2-(2-methoxyethoxy)ethyl methacrylate] (PMEO₂MA) with a lower critical solution temperature (~31°C) in aqueous medium was not soluble in water at 37°C. Poly[2-(tert-butylaminoethyl) methacrylate] (PTA) with a pKₐ about 9.2 could exhibit high bactericidal activity, because the tert-butylamino groups would be protonated in acidic bacterial infectious sites. Therefore, the water-soluble vesicles could be formed by the diblock copolymer (PMEO₂MA-b-PTA) dissolved in acidic aqueous solution when the solution temperature increases to 37°C. They observed these vesicles were demonstrated outstanding antibacterial activities to both S. aureus and E. coli.

5 CONCLUSION AND OUTLOOK

The rapidly increasing antibiotic resistance has become a critical issue and is responsible for the failure of conventional antibiotic therapy. In order to decrease the harm caused by bacterial infections with serious antibiotic resistance, people had intended to develop much more novel antibiotics. However, it is regrettable that the speed of development of antibiotic resistance has outdistanced the speed of antibiotic discovery at present. In this case, some bacterial infectious diseases with strong antibiotic resistance are becoming refractory at present. If no measure is taken, more bacterial infection with serious antibiotic resistance will be beyond remedy by any antibiotics in the future. Considering the serious situation of antibiotic resistance, WHO has proclaimed that the postantibiotic era has already come since 2013 all over the world.

The drug resistance of bacterial infections can be divided into two categories. The first category is the drug resistance caused by the formation of biofilm. Compared with planktonic bacteria, the bacteria in biofilm are usually...
in the state of low activity or dormancy, leading to the greatly decreased susceptibility of bacteria to antibiotics. Moreover, the impedance of biofilm EPS and the enhanced QS among bacteria are also the important reasons for the antibiotic resistance of biofilm. The second category is the drug resistance caused by bacterial self-evolution and mutation under antibiotic selection pressure. For example, under the long-term selection of methicillin, *S. aureus* evolved to MRSA, whose genes and structures were obviously different from *S. aureus*.

Due to the outstanding physicochemical properties, excellent delivery ability and bactericidal ability, nanomaterials are demonstrated to be attractive for enhancing the antibiotic therapy or acting as bactericidal agents to treat bacterial infections directly. The main treatment strategies contain antibiotic therapy and nonantibiotic therapy. The antibiotic therapy here is different from the conventional antibiotic therapy that employs antibiotic alone. The antibiotic therapy here is a therapeutic method that combines antibiotics and nanomaterials to destroy the mechanism of drug resistance, such as decomposing biofilm EPS, decreasing biofilm hypoxia, disturbing bacterial membrane, and so on. This kind of antibiotic therapy showed better bactericidal efficacy at same antibiotic concentration compared with the conventional antibiotic therapy. Some nanomaterials, such as silver nanoparticles, bronze nanoparticles, and polymeric nanoparticles with strong positive charge, showed excellent broad-spectrum bactericidal ability, thus they can act as important therapeutic method of nonantibiotic therapy. Additionally, due to the excellent thermal damage and oxidative damage, photothermal therapy and photodynamic therapy are also typical representatives of nonantibiotic therapy. Because no antibiotic is used in the therapeutical process, the nonantibiotic therapy is not only difficult to result in further antibiotic resistance, but also good for overcome antibiotic resistance. There is no doubt that both antibiotic therapy assisted by nanomaterials and nonantibiotic therapy induced by nanomaterials bring about new hopes to treat bacterial infections with strong antibiotic resistance.

Although nanomaterials exhibit enormous advantages and potentials to serve as novel antibiotic sensitizers or antibacterial agents, much work still remains to be done. For example, the long-term cytotoxicity and metabolism of some nanoparticles remain unknown. Understanding the mechanism by which each kind of nanoparticle functions at the cellular level is crucial for avoiding possible adverse side effects. Whatever, we hope that this review will help readers to understand a sense of the great potentials of nanomaterials for their possible applications in the treatment of drug-resistant bacterial infections.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

**ACKNOWLEDGMENTS**

Financial supports from Nature Science Foundation of China (51933009) and National Key Research and Development Program of China (2017YFB0702500) are gratefully acknowledged.

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coating technology. Several innovative techniques have been applied to biomedical devices including cardiovascular stent and catheter and so forth.

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**How to cite this article:** Hu D, Zou L, Gao Y, Jin Q, Ji J. Emerging nanobiomaterials against bacterial infections in postantibiotic era. *VIEW*. 2020;1:20200014. [https://doi.org/10.1002/VIW.20200014](https://doi.org/10.1002/VIW.20200014)