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MINIREVIEWS

Diagnosis and treatment of chronic osteomyelitis based on nanomaterials

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Abstract

Chronic osteomyelitis is a painful and serious disease caused by infected surgical prostheses or infected fractures. Traditional treatment includes surgical debridement followed by prolonged systemic antibiotics. However, excessive antibiotic use has been inducing rapid emergence of antibiotic-resistant bacteria worldwide. Additionally, it is difficult for antibiotics to penetrate internal sites of infection such as bone, thus limiting their efficacy. New approaches to treat chronic osteomyelitis remain a major challenge for orthopedic surgeons. Luckily, the development of nanotechnology has brought new antimicrobial options with high specificity to infection sites, offering a possible way to address these challenges. Substantial progress has been made in constructing antibacterial nanomaterials for treatment of chronic osteomyelitis. Here, we review some current strategies for treatment of chronic osteomyelitis and their underlying mechanisms.

Key Words: Osteomyelitis; Nanomaterials; Infectious disease; Drug delivery

Core Tip: Chronic osteomyelitis is a painful and serious disease caused by infected surgical prostheses or infected fractures. Traditional treatment includes surgical debridement followed by prolonged systemic antibiotics treatment. But as antibiotics is difficult to penetrate into the internal infection areas of bone, thus limiting the efficacy of systemic antibiotic therapy, new therapeutic approach to treat this disease remains a major challenge for orthopedic surgeons. Substantial progress has been made in constructing antibacterial nanomaterials for treatment of chronic osteomyelitis. We review some current strategies for treatment of chronic osteomyelitis and their underlying mechanisms.

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INTRODUCTION

Pyogenic osteomyelitis is the inflammation of bone tissue caused by pyogenic bacterial infection, including bone marrow, bone cortex, periosteum, and surrounding soft tissue infections, confined to one site or distributed throughout the body. The infection types are as follows: (1) Blood-borne infection: Pathogenic bacteria are transferred from distant infection foci to the bone tissue through the blood circulation, which is termed as bloodborne osteomyelitis; (2) Post-traumatic infection, also known as post-traumatic osteomyelitis, includes direct contamination of open fractures or bone infection after fracture surgery, especially after internal fixation or prosthesis implantation; and (3) Adjacent infection: Foreign body infection, pressure ulcers, and other adjacent soft tissue infections spread to the bone tissue, ulcers caused by diabetes and arteriosclerosis, and osteomyelitis caused by tissue necrosis. The most common site in children is the metaphysis of the long bones (distal femur and proximal tibia), or penetrating bone injury due to trauma[1-4]. Pyogenic osteomyelitis can be divided into acute and chronic types according to disease progression. It is speculated that the formation of dead bone is asign of chronic osteomyelitis as it appears 6 wk after disease onset[5,6].

OSTEOMYELITIS

Epidemiology of osteomyelitis

The incidence of osteomyelitis has increased with the upgrade of diagnostic technology, increase in prosthetic implants in orthopedic surgery, and increase in diabetes. For example, German researchers conducted statistical analysis of patients with osteomyelitis and found that, compared with 10 years ago, the overall incidence of osteomyelitis rose from 15.5/100000 people/year to 16.7/100000 people/year, an increase of 10.44%; however, this number was higher in developing countries and lower in undeveloped countries[1,7,8]. Kremers *et al*[9] assessed osteomyelitis from January 1969 to December 2009 and found that the total annual incidence of osteomyelitis was 21.8/100000 people/year. Nonetheless, the annual incidence of osteomyelitis was lower in women than in men and the infection rate increased with age. The incidence increased significantly from 11.4/100000 person-years in 1969-1979 to 24.4/100000 person-years in 2000-2009. The rates were stable in children and young adults but almost three times higher in those aged > 60 years, which could be attributed to a large increase in cases of diabetes-related osteomyelitis[10], of which, 44% had *Staphylococcus aureus* (*S. aureus*) infection. Lindbloom *et al*[11] investigated diabetic-foot-related osteomyelitis and found that diabetic foot infection was 36.5 per 1000 people/year, and the incidence of diabetic foot ulcers was 25%. About 20%-68% of diabetic foot ulcers are potentially associated with osteomyelitis. The amputation rate after osteomyelitis in diabetic foot infection is 66%. In one study, diabetes was associated with a 1.6% in-hospital mortality rate for osteomyelitis[12].

Common pathogenic bacteria of osteomyelitis

Among many pathogenic bacteria, *S. aureus* is the most common cause of chronic osteomyelitis[13,14]. However, specific bacterial distribution and drug resistance may vary across some regions due to patterns of use of antibacterial drugs in different areas. Data from southwest China were as follows: 467 cases (92.8%) had antibiotic treatment before admission, 324 cases (64.4%) were positive for culture, and 377 strains of microorganisms were cultivated. *S. aureus* (159 strains) accounted for 42.2%, and 38 strains were methicillin-resistant *S. aureus* (MRSA). There were 49 strains of *Pseudomonas aeruginosa* (*P. aeruginosa*) (13.0%), 35 of *Enterobacter cloacae* (*E. cloacae*) (9.2%), 33 of *Escherichia coli* (*E. coli*) (8.8%), seven of fungi (1.9%), 17 of *Acinetobacter baumannii* (4.5%), and 77 other microorganisms (20.4%)[15]. Jiang *et al*

[16] retrospectively analyzed 394 patients with chronic osteomyelitis of limbs treated in the Nan Fang Hospital from January 2010 to April 2015. The study cohort comprised 307 men and 87 women at a sex ratio of 3.53. The mean age at initial visit of all patients was 42 years. The positive rate of intraoperative culture was 70.63% (214/303), of which a single-strain infection accounted for 78.97% (169/214). Most of the single-strain infections were *S. aureus* (59 cases), while a few were *P. aeruginosa* (29 cases) or *E. coli* (11 cases). From January 1, 2012 to December 31, 2015, 5268 patients with limb fractures were admitted to this hospital, and 108 cases were diagnosed as post-traumatic osteomyelitis[16]. The bacterial cultures were positive in 77.8% (84/108) of patients. Among them, 104 microbial strains were detected, including 56 Gram-positive bacteria (53.9%), 39 *S. aureus* (37.5%), and six *Staphylococcus epidermidis* (*S. epidermidis*) (5.8%). There were 48 Gram-negative strains (46.1%), including 16 (15.4%) *E.coli* and 11 (10.6%) *E. cloacae* [17]. Another study showed that most bacteria, such as *S. aureus*, *P. aeruginosa*, *S. epidermidis*, and *Streptococcus pneumoniae*, adhere to the contact surface after invading the host[18]. There are even rarer cases of osteomyelitis being caused by *Salmonella*[19,20]. Surface anchoring proteins play a critical role in host cell adhesion and invasion, biofilm formation, and secretion of polysaccharide matrix, fibrin, and lipoprotein[21], which form an organized microbial aggregate biofilm[22]. This makes the bacteria resistant to the immune system[23]. Also, it is difficult to remove the biofilm completely with antibiotics, but the antibiotics kill the free bacteria in the blood that cause outbreaks of infection. When the body's resistance is reduced, the bacteria living in the biofilm are released, causing repeat infection. Biofilms are like shelters for microorganisms, leading to repeated outbreaks of chronic infection, which are prolonged and unhealed[24,25].

The interaction between osteoblasts and osteoclasts tightly regulates bone remodeling. The osteoblasts and osteoclasts communicate through direct contact between the cells or by secreting proteins that regulate their behavior, survival and differentiation[26]. *In vitro* studies have shown that bone tissue in an inflammatory and infective environment increases osteoclast activity and decreases osteoblast activity[27]. Biofilm-derived factors can decrease osteoblast activity by activating apoptosis under biofilm formation[28]. SPA mainly upregulates the expression of NFATc1 and C-FOS by activating the mitogen-activated protein kinase pathway, thus promoting the formation of osteoclasts [29]. It also binds to tumor necrosis factor receptor 1, which is highly expressed in osteoblasts[30], and then activates the downstream nuclear factor-kB pathway, leading to interleukin (IL)-6 release[31].

Therefore, we must focus on the research and development of new technologies and materials for the bacteria that cannot be controlled by antibiotics to achieve precise delivery of the drugs into the capsule. A specific drug can directly destroy the capsule of the bacteria to overcome the current disadvantages (Figure 1).

Pathophysiological mechanism of osteomyelitis

Before the onset of acute bloodborne disease, acute osteomyelitis often appears before the onset of disease in parts of the body with different degrees of infection foci[32], such as the upper respiratory tract and open fractures. With improper handling or immunodeficiency, the infection can spread throughout the body *via* the blood circulation and bacteria with the oven, and the bloodstream of children's long bone epiphysis nourishing artery is slow. The blood vessels are dense, retaining the bacteria and allowing their multiplication[33]. Bacteria multiply in cancellous bone and cause a local acute inflammatory reaction, such as hyperemia, edema, and leukocyte infiltration. Subsequently, local intraosseous pressure increases, causing severe pain, and then leukocyte necrosis releases lysozyme to destroy trabecular bone matrix abscess as it expands in the direction of low pressure. The local foci of infection can spread to the surrounding articular structures through the Havelian and Volkmann canals, and vascular occlusion exacerbates osteonecrosis. The necrotic bone is surrounded by granulation and fibrous tissues and is retained for a long time, resulting in the formation of dead bone, where a dead cavity is formed, termed a bone defect[34]. Often the course of osteomyelitis changes from acute to chronic. If the periosteum is not destroyed by infection, inflammation stimulates the formation of new bone beneath the periosteum, which can wrap around the dead bone and its upper and lower living segments. The dead bone and pericarp can cause the infected lesions to persist. Chronic osteomyelitis is likely to result from acute childhood osteomyelitis, followed by post-traumatic osteomyelitis, which causes bacterial colonization of bone tissue during open injury (Figure 2). In patients with reduced immunity, diabetes, atherosclerosis, and other conditions, the incidence of the disease is significantly increased.

In case of poor control of the lesion, the infection is surrounded by dead bone with no vascular supply, thickened periosteum, and fibrous tissue, eventually forming a zone of isolation. This isolation band can prevent the antibiotics from reaching this avascular region to kill the bacteria. Since the body's immune system cannot work correctly, it can easily lead to failure of drug treatment of osteomyelitis [35]. The lesions can exist for a long time and have intermittent episodes. If these persist for an extended period, they may become resistant to antibiotics[36]. In the face of intelligent bacteria, we must immediately find new materials that can fill bone defects, accurately deliver antibiotics to lesions, and assess auxiliary bactericidal and antibacterial effects.

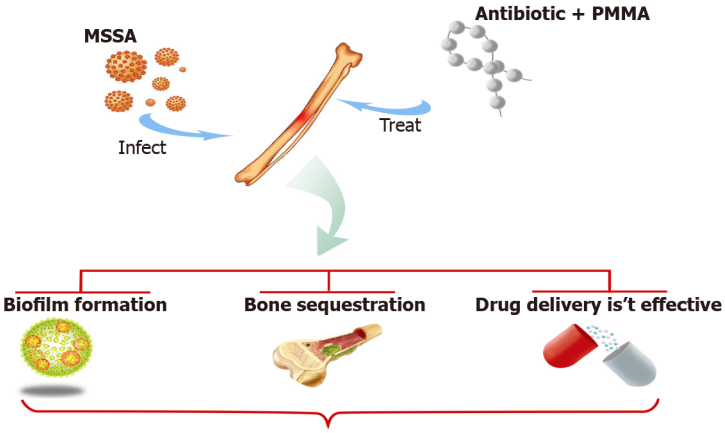

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Figure 1 A schematic of major challenges in the treatment of osteomyelitis. MSSA: Methicillin-susceptible *Staphylococcus aureus*; PMMA: Polymethyl methacrylate.

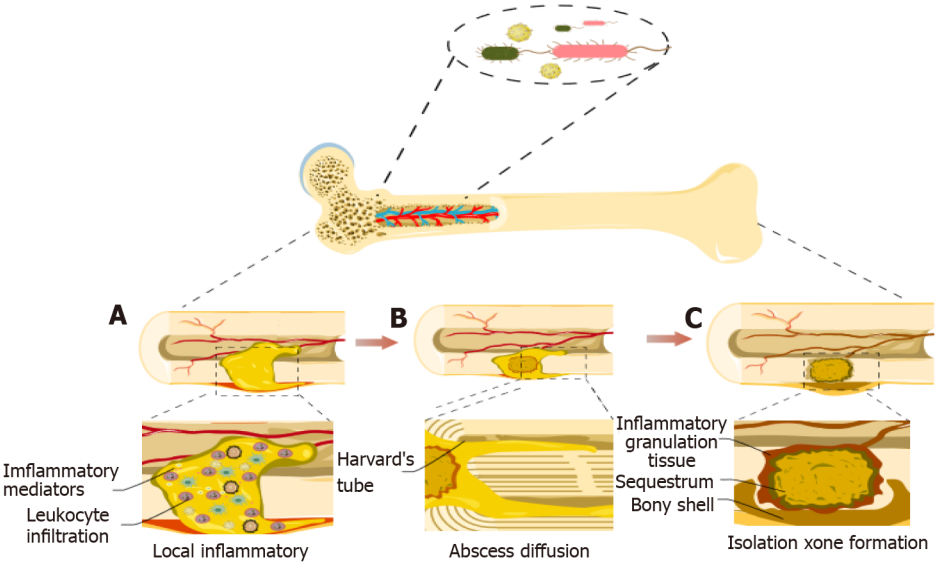

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Figure 2 Pathophysiological mechanism of osteomyelitis. A: Leukocyte necrosis releases inflammatory mediators to destroy bone matrix and bone trabeculae, forming abscesses; B: The infected lesions spread to the adjacent bone structures through Harvard's tube, and the intraosseous pressure is increased; C: Bone destruction and vascular obstruction resulted in different degrees of osteonecrosis and encapsulation.

NANOMATERIALS FOR DIAGNOSIS AND TREATMENT OF OSTEOMYELITIS

Nanotechnology is defined as the ability to translate the theory of nanoscience into practical applications by observing, measuring, manipulating, assembling, controlling, and manufacturing matter at the nanoscale (1-100 nm)[37]. After decades of rapid development, nanotechnology has achieved excellent results in other industries, and human life has become more convenient[38]. During this period, scientists have shown significant interest in the medical application of nanomaterials. Since nanomaterials are of similar size as biological molecules, all kinds of materials can be designed as carriers with a variety of functions that allow nanomaterials to pass through the capillaries in the human body or through the cells to regulate cell behavior and genes[39]. Therefore, nanotechnology has potential medical applications[40]. In recent years, many researchers have proposed nanomaterials for treating osteomyelitis to overcome a series of previously encountered problems (Table 1). It has been found that nanomaterials have many advantages in the treatment of osteomyelitis[41].

Nanomaterials for the diagnosis of osteomyelitis

Osteomyelitis has an insidious onset. Current imaging techniques make it challenging to make an accurate and specific diagnosis of osteomyelitis, which needs to be differentiated from other diseases, such as bone metastases, nonspecific inflammation, and Charcot arthropathy. Early osteomyelitis

Table 1 Application of novel nanomaterials in the treatment of osteomyelitis

Ref.	Material	Conclusion	Application
Bruna *et al* [46], 2021	Silver nanoparticles	With antibacterial agents as organic compounds or antibiotics it has shown synergistic effect against pathogens bacteria such as *Escherichia coli* and *Staphylococcus aureus*	Treat infections or prevent them efficiently
Zheng *et al* [57], 2018	Gold nanoclusters	Exhibit excellent treatment effects in both macrophages and animal infection models induced by MRSA as representative	Inhibition of MRSA biofilm formation. The induction of intracellular ROS production in bacterial cells
Gowri *et al* [68], 2021	Ca-Alg nanoparticle	Clindamycin loaded Ca-Alg/PPAA system showed sustained Clindamycin release from the carrier. Exhibited better cell viability of synthesized materials against MG63 cells	Sustained drug release. Promotes bone regeneration
Krishnan *et al*[69], 2020	Silica coated nanohydroxyapatite-gelatin reinforced with poly-l-lactic acid yarns	The nanocomposite fibrous scaffold containing vancomycin can be proposed as a bifunctional graft that can reduce bacterial infection, while subsequently engineer new bone in osteomyelitis	Reduce bacterial growth engineer. New bone in osteomyelitis
Hassani Besheli *et al* [71], 2017	Silk fibroin nanoparticles	The VANCO-loaded silk fibroin nanoparticles entrapped in scaffolds reduced bone infections at the defected site with better outcomes than the other treatment groups	With good biocompatibility and sustained release properties
Mahon *et al* [75], 2020	BMnP	In-house generated BMnP preferentially polarize human macrophages towards an M2 phenotype, activate the transcription factor cMaf and specifically enhance production of the anti-inflammatory cytokine, IL-10	Driving pro-angiogenic responses in human macrophages and HUVECs. Promoted M2 macrophage polarization, tissue vascularization and increased bone volume
Chen *et al* [58], 2021	Aptamer-functionalized platinum nanozymes	The activity switching and enhanced antibacterial effect of the nanocapsule were verified *in vitro* and in diabetic wounds	Catalyzing H_2O_2 into OH. Chemodynamic sterilization

Ca-Alg: Calcium-Alginate; BMnP: Bone mimetic nano hydroxyapatite particles; IL: Interleukin; HUVECs: Human umbilical vein endothelial cells; ROS: Reactive oxygen species; PPAA: Phosphorylating polyallylamine; MRSA: Methicillin-resistant *Staphylococcus aureus*.

patients are not identified by X-ray lesions as symptoms usually appear 10-14 d after infection. Without timely treatment for osteomyelitis, most cases progress to chronic osteomyelitis, making diagnosis and treatment complex and painful. Therefore, improving the accuracy of early imaging of osteomyelitis has become essential to managing this disease.

Superparamagnetic iron oxide nanoparticles (SPIONs)-ferumoxytol have been approved by the United States Food and Drug Administration for clinical application, and they can be absorbed in lymphatic tissue and bone marrow with < 20-nm lesions. In preliminary animal studies, Tsuda *et al*[42] and Fukuda *et al*[43] found that ferucarbotran was able to identify and diagnose bone metastases. Hence, they performed controlled clinical trials, in which patients with injection of SPIONs had significantly lowered signaling in bone metastases (-12.2%), osteomyelitis (-35%) or normal bone marrow (-46.6%). This indicates that SPIONs have the potential to differentiate bone metastases from osteomyelitis. Xiao *et al*[44] prepared uniform and bio-efficient IL-13-TAMRA-Gd3N@C80(OH)30-(CH2CH2-COOH)20 nanoparticles, which are a novel gadolinium cluster-coated metal-fullerenes (Gd3N@C80) obtained by coupling with IL-13 fragments. In a mouse model of chronic post-traumatic osteomyelitis, this novel nano-targeted probe specifically bound lipopolysaccharide to stimulate macrophages, which showed a high signal on the T1-weighted sequence of infection foci. This suggested that this novel targeted magnetic resonance imaging probe detected and distinguished CPO from sterile inflammation. Quantum dots (QDs) comprise a type of low-dimensional semiconductor material with photostability. They are a new fluorescent probe that can be used for biomolecular and cell imaging. Yousefi *et al*[45] used intermittent fluorescence emission (optical scintillation), electron density, and biocompatibility of QD nanoparticles. The combination of two different color QDs (red and green) can be used to distinguish osteomyelitis from Charcot neuroarthropathy.

Nanomaterials for sterilization

We have found that nanomaterials have many antibacterial properties and specific characteristics, and silver and silver nanoparticles (Ag-NPs) have been used as antibacterial agents. These nanoparticles exhibited antibacterial properties against various microorganisms (*P. aeruginosa*, *S. aureus* and *Vibrio cholerae*)[46]. The prevailing view is that, based on the microscopic properties of Ag-NPs, Ag^+ infiltrates the bacteria through the cell wall, causing the cell wall to rupture and increase cell permeability[47].

The respiratory chain in the intima is modified to produce reactive oxygen species (ROS) and free radicals that cause protein denaturation. The positively charged Ag^+ can bind to the negatively charged cell membrane[48]. Aurore *et al*[49] found that Ag-NPs enhanced the cytotoxicity of osteoclasts to MRSA, *P. aeruginosa*, and other microorganisms, and increased the reaction of free radicals to pathogenic microorganisms. Nandi *et al*[50] demonstrated that high-dose Ag-NPs had a good effect on the treatment of infection in an animal model of osteomyelitis but caused no toxicity to other significant organs. Wang *et al*[51] found that Ag-NPs inhibited biofilm formation of pathogenic microorganisms and reduced bacterial adhesion by regulating expression of bacterial genes (*ICAR* and *ICAA* of *S. epidermidis* and *fnbA* and *fnbB* of *S. aureus*). Secinti *et al*[52] confirmed that nanosilver ion coating inhibits biofilm formation on implants. Afzal *et al*[53] showed that addition of hydroxyapatite (HA) and carbon nanotubes (CNTs) to 5% Ag-NPs enhanced the bactericidal performance of these composites.

However, in mammalian cell models, the antimicrobial efficacy of Ag-NPs is largely due to the production of Ag ions, which are potentially cytotoxic to both target bacterial cells and normal host cells [54], posing a serious safety threat to practical clinical applications. We are also looking for other unique materials that do not attack indiscriminately. Unlike silver, gold is inert and does not readily decompose into ions to produce cytotoxicity, but it has been observed in mammalian models with high biocompatibility and low biotoxicity. The biological activity of Au-NPs has been studied for a long time. Due to the characteristics of stability and high biocompatibility, Au-NPs have become the optimal choice for nanocarriers[55]. When Au-NPs attach to the surface of the microbial cell wall, due to their inherent antibacterial properties, both bacteria and nanoparticles combine to produce physical and chemical surface modifications and produce ROS, which cause bacterial protein degeneration, DNA damage, mitochondrial dysfunction, and ultimately cell death[56]. Zheng *et al*[57] evaluated the effects of gold-4-amino-6-hydroxy-2-mercaptopyrimidine (Au-DAMP) on biofilm formation and maturation in mice infected with MRSA. The results showed that Au-NPs had high anti-biofilm activity, and the formation of MRSA biofilm was inhibited significantly even at a low concentration of Au-NPs. Unlike other precious metal nanomaterials, Au-DAMP can eliminate MRSA mature biofilms at low concentrations; a property not possessed by the most common antibacterial agents. Chen *et al*[58] prepared an activated nanocase with chemodynamic therapy. This new platinum nanocase and glucose oxidase were encapsulated in an HA shell and termed APGH nanocapsules (Figure 3). *In vitro* experiments demonstrated that the novel nanocapsule reduced the pH and H_2O_2 constraints. The nanocapsule retained peroxidase-like activity, making it suitable for antibacterial treatment and accelerating healing in diabetic wound models.

In addition to chemodynamic therapy, photodynamic therapy (PDT) nanomaterials have been widely used in diagnosing and treating tumors, but relevant studies have assessed the antibacterial effect of PDT. Kuo *et al*[59] performed water-soluble C60 (OH) 30 on Gram-positive MRSA to prove that nanomaterial photochemokinetics also effectuate sterilization. In this study, ROS were produced using water-soluble fullerenol, and PDT killed most Gram-positive bacteria within a short period. Faced with the challenge of the increase in drug-resistant bacteria worldwide, scientists are looking for ways to replace or enhance the sterilization effect of antibiotics. Some scientists have started innovative research on the mechanism of action of magnetic nanomaterials on bacteria. The hyperthermic effect induced by low-intensity magnetic fields destroyed the bacterial biofilm and promoted absorption of antibiotics [60]. Hyperthermia has been evaluated in clinical trials for prostate cancer and glioma with remarkable results and no severe side effects[61,62]. By embedding the heating source into the tissue, magnetic particle hyperthermia uses an external alternating magnetic field to increase the accuracy and reduce the occurrence of damage to the surrounding normal cells. Magnetic particle hyperthermia improves the accuracy of heating. Fang *et al*[60] used magnetic nanoprecision-induced hyperthermia to destroy the bacterial biofilm of infected lesions, thus improving the sterilization effect of antibiotics. Fe_3O_4 nanoparticles implanted into a rat model of osteomyelitis were heated to 75 °C by magnetic heating, which did not cause tissue loss but could destroy the biofilm polysaccharide matrix to enhance the permeability of the antibiotics.

A previous study discovered carbon-based nanomaterials, such as graphene and CNTs[63]. Because of its unique structural characteristics and physical and chemical properties, carbon-based nanomaterials have high antibacterial activity. Embedded in the phospholipid bilayer, the phospholipid membrane structure and phospholipid molecular configuration are disturbed, which directly or indirectly achieve a bactericidal effect or oxidize bacterial molecules, such as lipids and proteins, through the generation of oxidative stress *via* ROS[64].

Nanomaterials for drug delivery

The main goal of our nanotechnology application is to load the treatment unit into the nanocarrier and transport the therapeutic drugs to a lesion without leakage, which increases the local concentration of the drug. Eventually, the disease-causing organism is destroyed because the carrier acts like a precision-guided missile to deliver a precise strike to the target. The standard treatment for osteomyelitis consists of thorough debridement of the infected bone-removal of dead bone and elimination of dead cavities-followed by long-term systemic antibiotic therapy based on bacterial culture results[65]. The major challenge to this method is how to keep the normal bone tissue while maintaining complete debridement to avoid nonunion, limb dysfunction, and pathological fracture. Furthermore, long-term

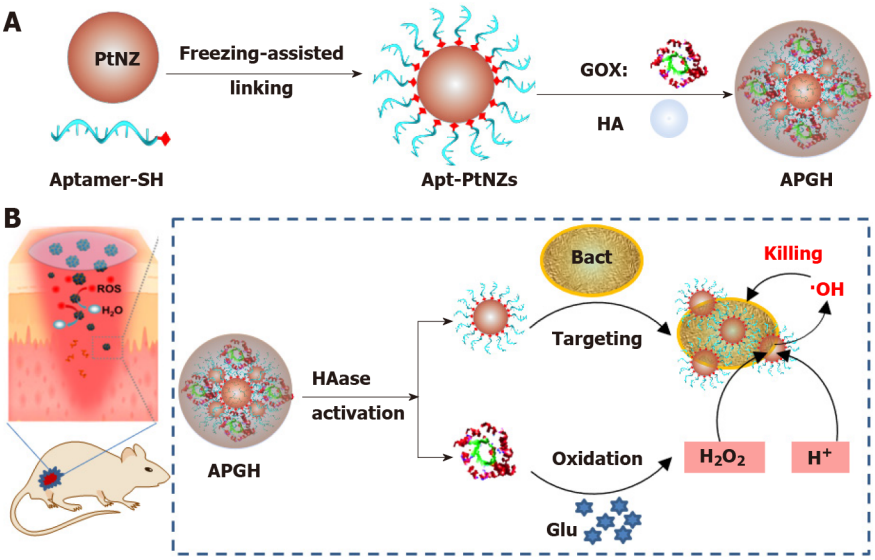

Figure 3 The illustration of APGH released the Aptamer-functionalized platinum nanozymes and glucose oxidase and its application for chemodynamic sterilization. A: The preparation route for the nanozyme capsule (APGH) with aptamer-functionalized platinum nanozymes, glucose oxidase and hyaluronic acid; B: Schematic illustration of APGH activation, activity switching in the infected wound, and its application for chemodynamic sterilization through *in situ* generation of COH on bacteria surface. Apt-PtNZ: Aptamer-functionalized platinum nanozymes; HA: Hyaluronic acid; GOX: Glucose oxidase. Citation: Chen L, Xing S, Lei Y, Chen Q, Zou Z, Quan K, Qing Z, Liu J, Yang R. A Glucose-Powered Activatable Nanozyme Breaking pH and H_2O_2 Limitations for Treating Diabetic Infections. *Angew Chem Int Ed Engl* 2021; 60: 23534-23539. Copyright ©The Author(s) 2021. Published by John Wiley and Sons. The authors have obtained the permission for figure using from the John Wiley and Sons and Copyright Clearance Center (Supplementary material).

systemic use of large doses of antibiotics can easily lead to antibiotic resistance and side effects, such as rashes, abdominal pain, and other gastrointestinal reactions. However, it is difficult for antibiotics to reach the osteomyelitic focus, resulting in insufficient local drug concentration and delayed healing.

Hence, we altered the treatment approach by filling the locally infected site with polymethyl methacrylate (PMMA) bone cement and microbeads loaded with antibiotics. The advantage of this approach is that it facilitates the delivery of a high concentration of the drug to the local infection site while reducing systemic toxicity. However, the PMMA bone cement delivery system also has some deficiencies in the treatment of osteomyelitis: (1) Heat generated during the preparation of PMMA implants affects the activity of loaded drugs; (2) PMMA is expensive; (3) PMMA bone cement cannot be absorbed in the body, requiring a second operation forits removal; (4) PMMA stents cannot achieve sustained drug release, and the drug release kinetics are poor; and (5) After the release of the loaded antibiotics, the remaining PMMA scaffold may become a site for bacterial determination[66]. Recent animal experiments and clinical applications show that nanoparticles have potential compared with existing drugs because of the size of nanoparticles that can enter pathogenic microorganisms or bone cells. Currently, we are exploring ways to target the drugs into specific bone sites, reducing costs, and improving compliance by maximizing controlled drug release such that the required drug concentration can be maintained over an extended period without exceeding toxicity levels or dropping below the minimum effective dose. Nanoparticles can deliver drugs through two mechanisms: (1) Nanoparticles bind to the microbial cell wall/membrane or osteoblast cell wall/membrane to release drugs into the cytoplasm; and (2) Nanoparticles can attach to the cell walls and act as drug repositories to continuously release the drug, which can then spread into the cell[67].

Currently, a variety of nanomaterials suitable for drug delivery for the precise treatment of osteomyelitis are being developed. Gowri *et al*[68] prepared calcium alginate (Ca-Alg) nanoparticles by salting out and loading clindamycin after crosslinking and phosphorylating polyallylamine (PPAA). The *in vitro* drug release experiments showed that the Ca-Alg/PPAA system had a sustained-release effect. The results of trypan blue colorimetry and MTT cytotoxic colorimetry showed that the system had good biocompatibility with osteoblasts (MG63). The Ca-Alg/PPAA/clindamycin system can control the synthesis of microbial flagella, affect the growth rate of cells, and reduce the viability of cell colonies by inhibiting viability. Krishnan *et al*[69] produced vancomycin-supported nanocomposite fiber Scaffidi (silica-coated nano-HA gelatin matrix). The porous structure (average pore size 150-350 μm) provides a large surface area and absorbs a large volume of antibiotics. In male Wistar rats (250-350 g), vancomycin release of all composite scaffolds was 10-20-fold higher than the minimum inhibitory concentration within 30 d. Anagar diffusion test, turbidity test, and bacterial adhesion test showed an excellent antibacterial effect, which could remove bacteria and promote the formation of new bone in 3 mo after implantation in a bone marrow disease model. Zhou *et al*[70] showed that mesoporous silica nanoparticle gelatin matrix composite fiber scaffold loaded with vancomycin promoted bone healing and significantly reduced bacterial contamination. Hassani Besheli *et al*[71] demonstrated that a silk

fibroin nanoparticle delivery system had strong antibacterial effect, targeted delivery, and continuous release of drug activity in a model of severe osteomyelitis induced by MRSA injection into the tibia of male Wistar rats (260-330 g). Wan *et al*[72] prepared polyvinyl alcohol/polycaprolactone (PCL) nanocomposite film and combined it with cefuroxime sodium. They measured the drug release from the nanocomposite material by spectrophotometry and concluded that the system was simple to prepare and had good biocompatibility. The stable and slow release of the drug may cause reversible absorption of the drug in PCL and forma hydrophobic layer.

Nanomaterials for treatment of chronic osteomyelitis

According to the clinicopathological mechanism of osteomyelitis, we considered the selection of nanomaterials for treatment after the formation of dead bone. The severe infection environment reduces the self-repair ability of bone tissue and delays bone regeneration[73]. A large area of the bone defect is often formed in the bone marrow cavity. There may be nonunion, pathological fracture, and other severe complications in the absence of intervention. Presently, autologous bone transplantation or artificial bone is used for clinical intervention; however, this scheme cannot inhibit bacterial growth and has a prolonged prognosis. Therefore, it is crucial to find materials that can promote proliferation of osteoblasts, inhibit osteoclast activity, and serve as vectors for antibiotics. This approach ensures antimicrobial efficacy, thereby minimizing the risk of antimicrobial resistance and infection recurrence, and stimulates osteoblast differentiation and proliferation, thereby promoting the formation of healthy bone tissue.

Jiang *et al*[74] divided 45 rabbits with chronic osteomyelitis into experimental, control, and blank groups, and evaluated them by X-ray, biopsy, and microbial culture. Vancomycin-loaded nano-HA pellets controlled the infection and repaired bone defects caused by MRSA-associated osteomyelitis. No significant or isolated nano-HA was observed in the experimental group 3 wk after implantation. The particles were involved in the formation of bone trabeculae or were replaced by medullary luminal tissue, and new bone was formed around the implanted particles. After 6 wk, the bone in the experimental group returned to normal and the periosteal reaction was weakened. Mahon *et al*[75] studied how nano-hydroxyphospholime promoted bone regeneration. They demonstrated that bone mimetic nano hydroxyapatite particles (BMnPs) preferentially polarized the M2 phenotype of human macrophages and specifically enhanced the production of the anti-inflammatory cytokine IL-10. The secretion of BMnP-treated macrophages promoted mesenchymal stem cell osteogenesis in an IL-10-dependent manner, suggesting that BMnPs directly promoted the osteogenic effect. In addition, BMnP-treated rats had significantly increased bone volume and stimulated expression of osteogenic genes, bone morphogenetic protein 2 (BMP2) and alkaline phosphatase (ALP), suggesting that BMnPs promote bone regeneration. IL-10 promotes chondrocyte differentiation and proliferation through the BMP pathway, and recombinant IL-10 promotes the expression of BMP-2, alkaline phosphatase, and osteopontin. Westhauser *et al*[76] observed that zinc-loaded mesoporous bioactive glass nanoparticles (5Zn-MBGNs) promoted osteogenic differentiation and expression of genes related to the extracellular matrix (ECM), and significantly promoted the formation and calcification of ECM, suggesting an excellent osteogenic effect. These genes also increased ALP activity, promoted DNA synthesis, and significantly increased calcium deposition. 5Zn-MBGNs IDPS upregulated expression of *OCN* and *COL1A1* genes, which significantly promoted ECM formation and calcification. The novel chitosan nanohybrid hydrogel and scaffold materials prepared by Mahanta *et al*[77] were highly porous, open, and three-dimensionally interconnected. In a rat femoral defect model, the bone healing rate of the nanohybrid scaffold was faster compared with that of the pure chitosan scaffold, while the cell growth rate of the nanohybrid scaffold was faster, and the cell proliferation was rapid.

BMP-2 is the most widely studied BMP, with the strongest activity in inducing endogenous bone formation, and it exists as a 30-kDa molecule in the form of a dimer[78]. Recombinant human (rh)BMP-2 has been expressed by gene recombination technology; however, the osteogenic activity of rhBMP-2 is lower than that of natural BMP-2, and the ideal vector has not been identified. Therefore, the search for a new nanomaterial containing BMP-2 has become a new direction for treatment of bone defect caused by osteomyelitis. Qiu *et al*[79] preloaded BMP-2 onto mesoporous HANPs and synthesized it into silk fibroin/chitosan composite. The results showed that scaffolds loaded with BMP-2 had better cell adhesion, provided an ideal microenvironment for cell proliferation, and significantly increased bone formation. SCH scaffolds containing BMP-2 had more material absorption and bone trabecular deposition than non-BMP-2 scaffolds had. The mesoporous HANPs maintained continuous release of BMP-2. This mode of delivery preserves the bioactivity of BMP-2. Therefore, the osteogenic effect of the scaffold can be improved. Qiao *et al*[80] reported a microwave-excited antibacterial nanocapturer system for treating deep tissue infections that consisted of microwave-responsive Fe_3O_4/CNT and gentamicin (Figure 4). They suggested that Fe_3O_4/CNT/gentamicin efficiently targeted and eradicated MRSA-infected rabbit tibia osteomyelitis.

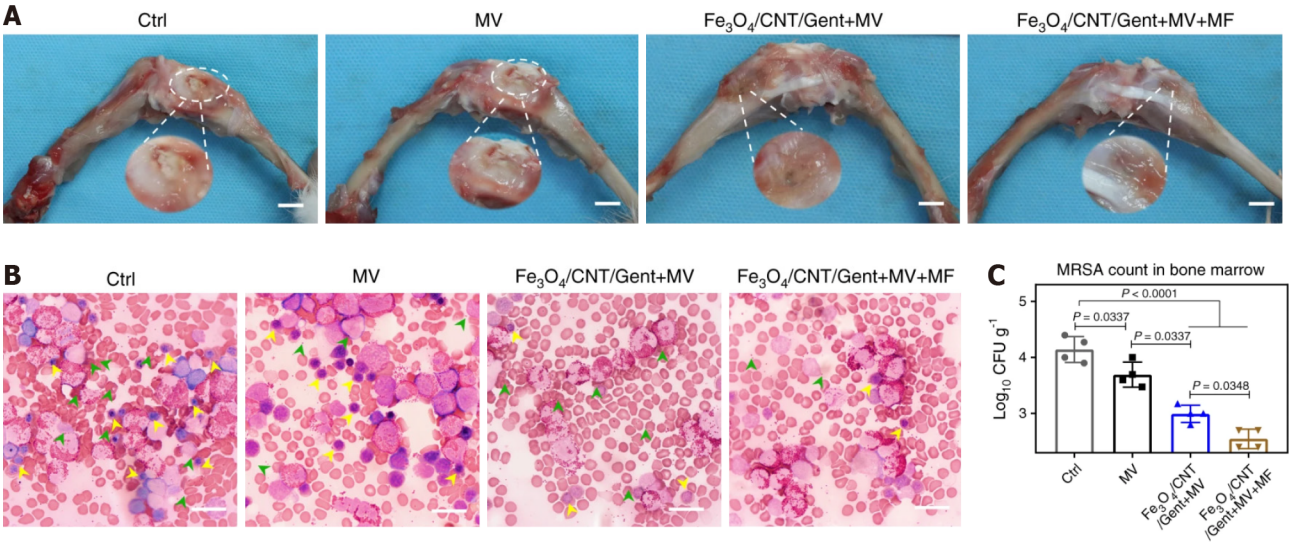

Figure 4 Antibacterial effects of Fe_3O_4/carbon nanotube/Gent on methicillin-resistant *Staphylococcus aureus*-infected osteomyelitis *in vivo*. A: Macro images of femur and tibia in each group of animal models 14 d after treatment. Scale bars = 1 cm; B: Wet-stained images, scale bars = 20 μm, 14 d after treatment; C: Methicillin-resistant *Staphylococcus aureus* count in bone marrow of each group after 2 d of antibacterial treatment. CNT: Carbon nanotubes. Citation: Qiao Y, Liu X, Li B, Han Y, Zheng Y, Yeung KWK, Li C, Cui Z, Liang Y, Li Z, Zhu S, Wang X, Wu S. Treatment of MRSA-infected osteomyelitis using bacterial capturing, magnetically targeted composites with microwave-assisted bacterial killing. *Nat Commun* 2020; 11: 4446. MRSA: Methicillin-resistant *Staphylococcus aureus*.

CONCLUSION

Continuous research and development of nanomaterial preparations have enhanced the therapeutic effect of nanomaterials on infection, including improved treatment of osteomyelitis. Our goal is to perfect the treatment of chronic osteomyelitis by using a variety of new nanomaterials, which cannot be reached by either common antibiotics or sustained-releasing antibiotics. Because of the material properties, nanomaterials have antibacterial activity with as low-releasing and bone regeneration promoting ability. Recent research has been limited to animal experiments and has not been applied to clinical treatment. Thus, we need to understand the toxic effects and metabolism of nanoparticles, their properties, and the cost of preparing these materials to consider whether nanomaterials are suitable for treating chronic osteomyelitis. These tasks require a multidisciplinary collaboration.

FOOTNOTES

Author contributions: Zeng M and Xu Z contribute equally to this study, they share co-first author; Xu Z wrote the paper; Zeng M and Li J did the literature review; Tang ZW and Song ZQ did the data analysis; Xiao S conceived and coordinated the study; Wen J revised the paper; and all authors reviewed the results and approved the final version of the manuscript.

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