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REVIEW

Advances in the Application of Multimodal Nano-Antimicrobial Strategies in Prosthetic Joint Infections: A Systematic Review

Ziming Zhang[1,*], Jianfeng Sun[2,3,*], Yan Luo[2,3], Cheng Huang[4], Wenfeng Xiao[2,3], Weiguo Wang[4]

[1]Xiangya School of Medicine, Central South University, Changsha, Hunan, People's Republic of China; [2]Department of Orthopedics, Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China; [3]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital of Central South University, Changsha, Hunan, People's Republic of China; [4]Department of Orthopaedic, China-Japan Friendship Hospital, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Wenfeng Xiao, Department of Orthopedics, Xiangya Hospital, Central South University, Changsha, Hunan, People's Republic of China, Email xiaowenfeng@csu.edu.cn; Weiguo Wang, Department of Orthopedics, China-Japan Friendship Hospital, Beijing, People's Republic of China, Email jointwwg@163.com

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Background: Prosthetic joint infection (PJI), a severe complication following total joint arthroplasty, is characterized by prolonged treatment duration, high costs, and poor outcomes. Current clinical treatment which typically relies on the use of antibiotic-loaded bone cement (ALBC) is limited by the generalization of bacterial resistance and the inherent defects of bone cement. Advancements in nanotechnology have led to nanomaterials and nanocoatings that offer promising alternative strategies, showing great potential for the prevention and management of PJI. This review aims to summarize the applications of nanotechnology in preventing and treating PJI following total joint arthroplasty and further discuss current advances and future perspectives in this field.

Methods: PubMed, Web of Science, Scopus and Embase were searched for relevant studies covering the period from their inception to June 12, 2025. After removal of duplicate records, studies were excluded based on their abstract and title. The remaining studies were assessed for eligibility based on their full-text content.

Conclusion: Nanotechnology has emerged as a highly promising alternative strategy against PJI. The current research frontiers encompass not only the development of stimulus-responsive nanomaterials for precise antibacterial control but also exploring their integration with targeted therapies, immunotherapy, and piezoelectric-based therapy.

Keywords: prosthetic joint infection, nanotechnology, nanomaterials, antibacterial

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Introduction

Total joint arthroplasty is frequently associated with postoperative complications, including dislocation, periprosthetic fracture, aseptic loosening, PJI, and venous thromboembolism.[1] Prosthetic joint infection (PJI) is a devastating complication of total joint arthroplasty, occurring in 1–3% of primary procedures. It accounts for 14.8% of revision total hip arthroplasties (THAs) and 25.2% of revision total knee arthroplasties (TKAs) and is associated with a five-year mortality rate of nearly 20%.[2–6] A total of 38.5% of patients experienced a deteriorated quality of life after PJI, encompassing physical or psychological aspects.[7] Furthermore, PJI treatment imposes substantial economic burdens, with mean per-case costs exceeding US$30,000 for both THA and TKA cases in most developed nations.[3,5,8] With the total cost per PJI of the hip case in the United States being approximately $390,000, the projected cumulative expenditure for PJI management is estimated to reach $1.85 billion by 2030.[4,8,9]

For early-stage PJIs with mild symptoms and a stable implant, debridement, antibiotics, and implant retention (DAIR) represent widely used treatment strategies.[10,11] Other clinically stable patients who do not meet the DAIR criteria require prosthesis removal, thorough debridement, and subsequent reimplantation of a new prosthetic component through either

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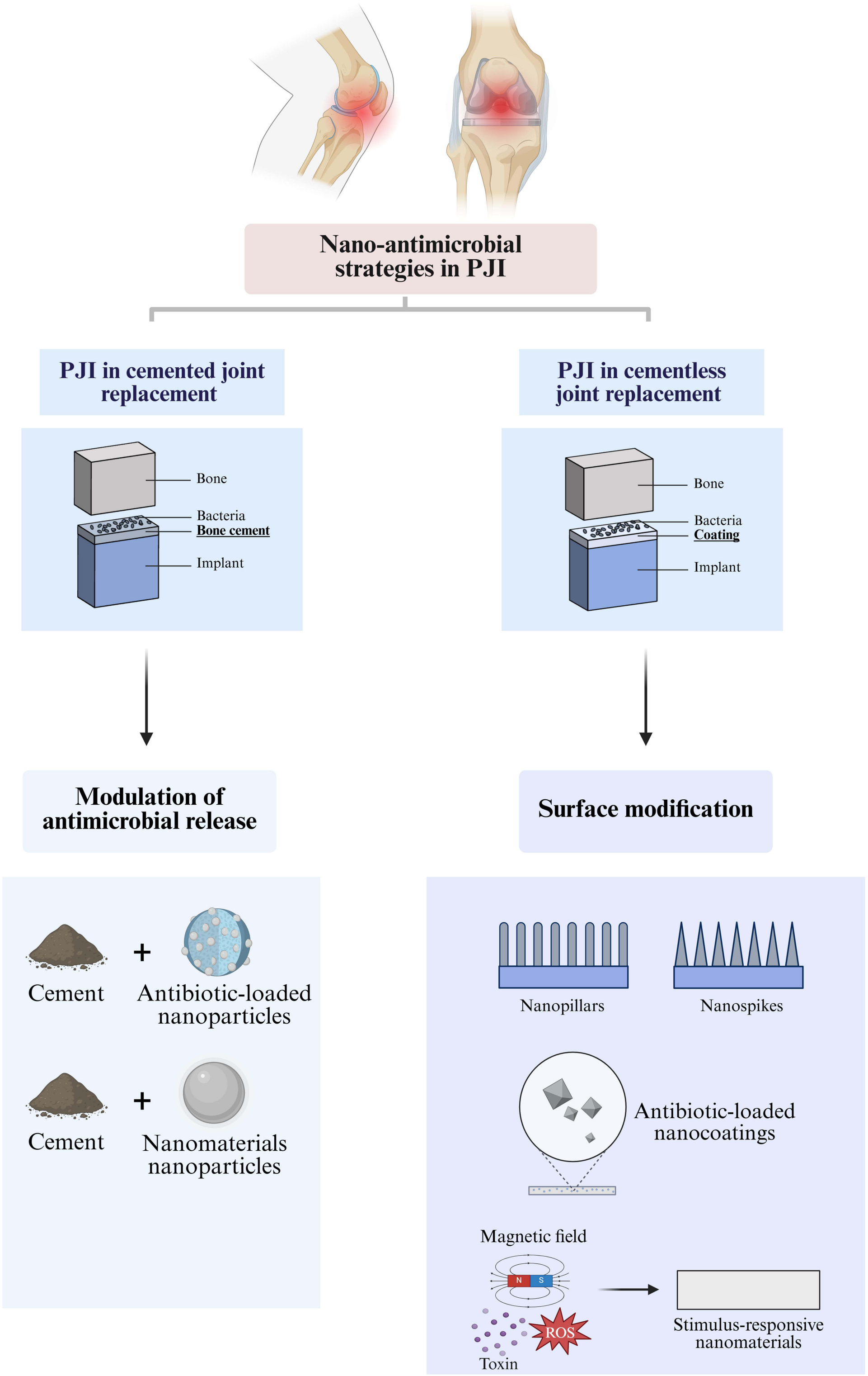
Graphical Abstract



one-stage revision or two-stage revision, and two-stage revision arthroplasty has become the gold standard for treating this patient population.[11–13] Owing to the limited antimicrobial efficacy of systemic antibiotic administration, local infections are frequently combated through the application of antibiotic-loaded bone cement (ALBC), which delivers higher concentrations of antibiotics into the articular cavity while demonstrating fewer adverse effects compared to systemic antibiotic administration.[14] ALBC has also been widely adopted in cemented arthroplasty as a prophylactic measure against PJI.[15] However, ALBC is limited by inconsistent antibiotic elution properties. Moreover, the problem of bacterial antibiotic resistance associated with prolonged clinical antibiotic application has become increasingly evident in recent years.[16,17] A 2019 surveillance study from England, Wales, and Northern Ireland reported that 59 out of 166 PJI cases were caused by gentamicin-resistant bacterial strains.[18] Similarly, a 2025 study by Jiang et al, investigating 255 PJI patients from China, isolated 335 pathogenic strains, of which 193 exhibited resistance to at least three clinically used antibiotics.[19] The suboptimal antibiotic elution properties of ALBC limit its antimicrobial efficacy to short-term therapeutic effects, and prolonged use not only fails to achieve effective bacterial eradication but may also promote the development of bacterial resistance.[20,21] Consequently, effective alternative antimicrobial strategies are needed.

With the increasing prevalence of drug-resistant bacteria, the advent of nanotechnology has not only enhanced conventional therapeutic approaches but also led to the development of novel alternative antibiotic strategies.[22–25] While maintaining acceptable levels of cytotoxicity, nanotechnology-based approaches can effectively inhibit bacterial growth and prevent biofilm formation on implant surfaces by enhancing local antibiotic delivery and utilizing mechanisms such as direct mechanical bactericidal activity, silver ion toxicity, and reactive oxygen species (ROS) generation.[16] Nanotechnology shows promising applications in the treatment of PJI. This review evaluates the modalities and mechanisms of nanotechnology in preventing and treating PJI associated with cemented and uncemented arthroplasty (Figure 1). Furthermore, these findings highlight the emerging antimicrobial applications of antimicrobial nanotechnology for PJI.

Methods

Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive search was performed in the electronic databases of PubMed, Web of Science, Scopus, and Embase to identify relevant studies published from their inception to June 12, 2025. The search strategy was developed by combining relevant keywords using the Boolean operators "AND" and "NOT". The keywords included "nano material", "nano particle", "nano coating", "nano structured", "nano therapeutic", "nano drug", "infection", "prosthetic joint infection", "antibacterial", "antimicrobial", "joint replacement", "arthroplast" and "prosthetic joint".

Eligibility Criteria

The inclusion criteria were as follows: (1) studies that simultaneously addressed PJI and nanotechnology-based antibacterial strategies; (2) studies that, while not directly involving PJI, offered methodological insights with potential relevance; and (3) all selected records must be investigational articles.

Conversely, studies were excluded for the following reasons: (1) studies not addressing PJI; (2) studies lacking nanotechnology-based antibacterial strategies; (3) studies that did not assess antimicrobial performance; (4) literature reporting on outdated antibacterial strategies that have been replaced by newer ones; (5) studies where the incorporated nanotechnology did not play a demonstrable role in enhancing antibacterial activity; and (6) non-research articles.

Study Selection

All identified records were imported into EndNote for duplicate removal. Subsequently, two independent reviewers screened the titles and abstracts of the remaining articles against the eligibility criteria. Articles that passed this initial screening underwent a full-text assessment by the same reviewers. Any discrepancies regarding the eligibility of a study were resolved through discussion or, if necessary, by consultation with a third reviewer to reach a consensus.

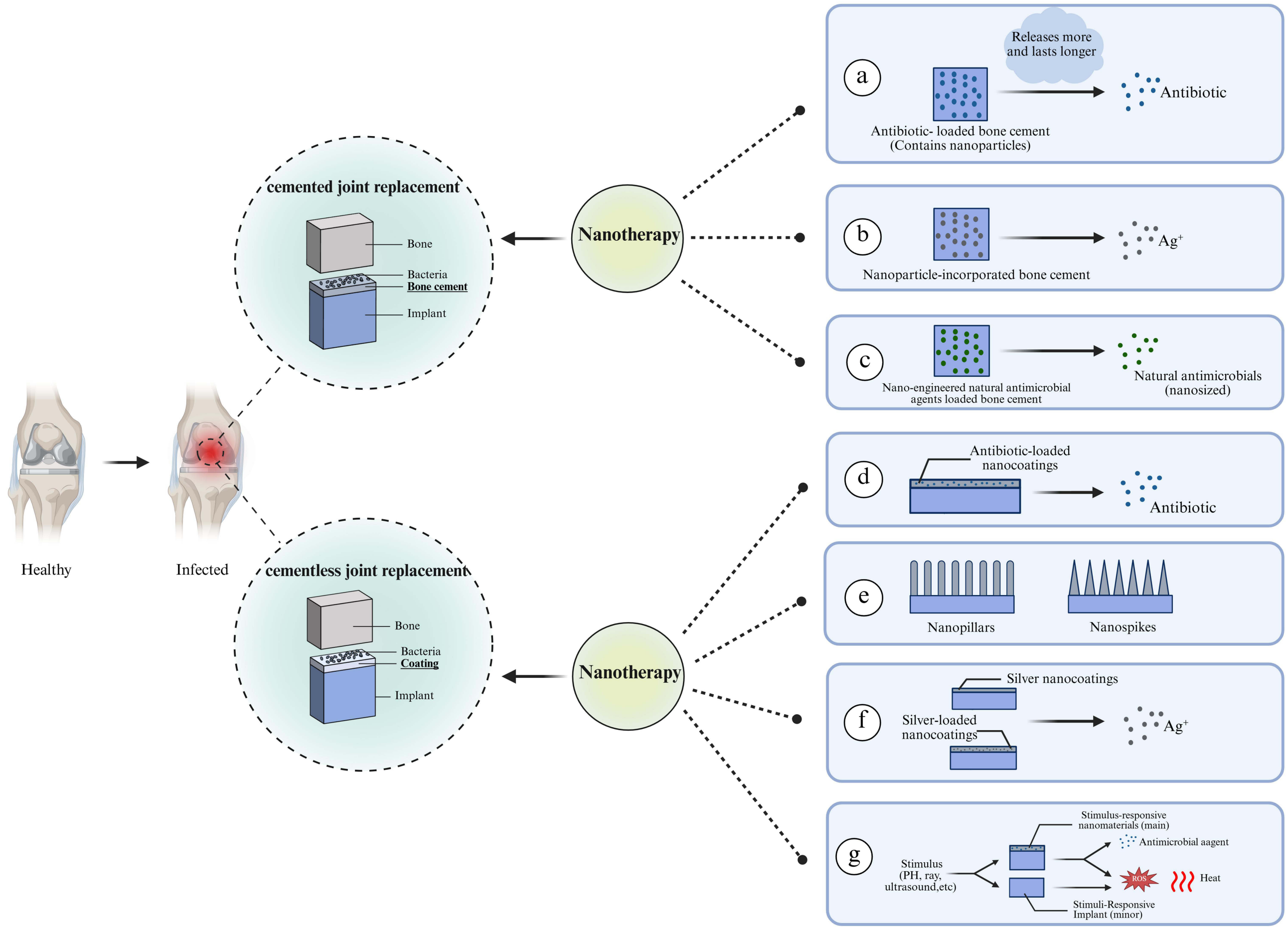


Figure 1 Classification of Nanotechnology-Based Antimicrobial Strategies for PJI: (**a**) Antibiotic-loaded nanomaterial-doped bone cement exhibits a superior release profile compared to conventional antibiotic-loaded bone cement, characterized by both a greater quantity released and a prolonged duration. Releasing more refers to a greater total amount of antibiotics released, which helps maintain the local antibiotic concentration above the Minimum Inhibitory Concentration (MIC). Lasting longer indicates a prolonged duration of substantial antibiotic release, resulting in an experimentally observable extension of the time during which the local antibiotic level remains above the MIC. Collectively, these two effects manifest as a higher cumulative release percentage of antibiotics from the nanoparticle-incorporated antibiotic-loaded bone cement compared to its nanoparticle-free counterpart. As can be clearly seen in the in vitro results of Thaher et al, the cumulative antibiotic release from gentamicin-loaded bone cement incorporating 3% CNTs was three times greater than that from conventional antibiotic-loaded bone cement.[26] (**b**) Nanoparticle-incorporated bone cement exerts antimicrobial effects through sustained silver ion release. (**c**) Bone cement loaded with nano-engineered natural antimicrobial agents, such as chitosan and curcumin, demonstrates antibacterial activity through the controlled release of nano-formulated natural antimicrobial agents. (**d**) Antibiotic-loaded nanocoatings exert antimicrobial effects through precise and controlled antibiotic release. (**e**) Nanostructured coatings exert mechanical antimicrobial effects through surface topography-mediated physical disruption. (**f**) Silver-loaded nanocoatings and silver nanocoatings exert antimicrobial effects through sustained silver ion release. (**g**) Stimulus-responsive nanomaterials exert antimicrobial effects through controlled antibiotic release, reactive oxygen species (ROS) generation, and photothermal activity, with their antibacterial efficacy precisely regulated by external triggers. The terms "Bone cement" and "Coating" serve to distinguish between cemented and cementless arthroplasty. This fundamental difference in surgical approach accordingly necessitates different strategies for treating subsequent PJI. Among these, strategies (**a–c**) focus on improving the antimicrobial properties of bone cement for application in cemented joint arthroplasty, while approaches (**d–g**) target the development of antimicrobial implant coatings primarily used in cementless arthroplasty, created in BioRender. Li, (Y) (2025) https://BioRender.com/b411082.

Results

After deduplication of the records retrieved from the four databases, 546 articles remained. We then screened these titles and abstracts, leading to the exclusion of studies that did not meet the content criteria or were not investigational articles. Following the exclusion of literature that did not meet the eligibility criteria, such as studies with unevaluated antimicrobial activity, obsolete or superseded antibacterial strategies, 23 articles were ultimately included in this systematic review (Figure 2).

Among the 23 included studies, 8 were in vivo investigations, with the remaining 15 being in vitro studies. 10 studies specifically focused on nanotherapeutic strategies for bone cement in arthroplasty, which included ALBC incorporated with nanomaterials, silver nanoparticles, and nanoengineered natural antimicrobial agents.[26–35] The other 13 studies, which focused on nanotherapeutic strategies for cementless arthroplasty, were categorized into the following groups:

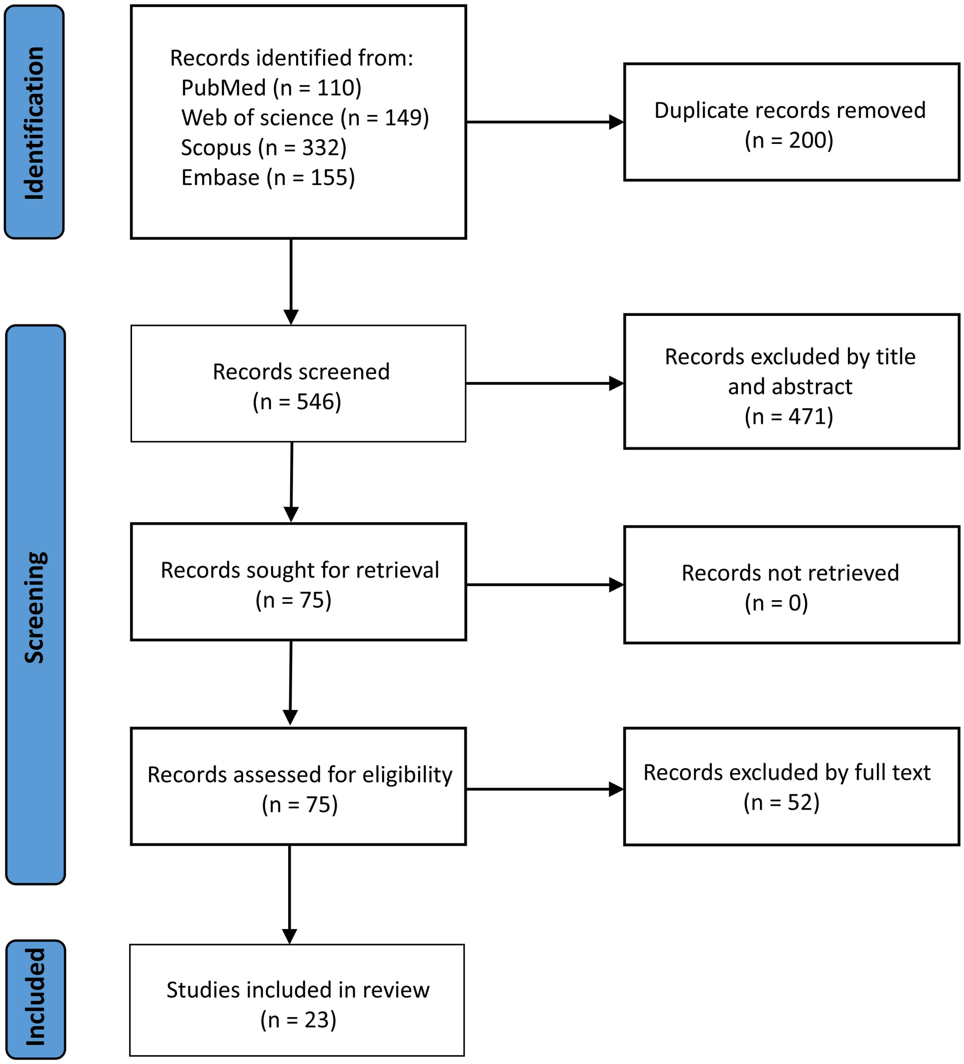


Figure 2 PRISMA flow diagram illustrating the literature search and study selection process.

antibiotic-loaded nanocoatings, stimuli-responsive nanomaterials for controlled antibiotic release, nanostructured coatings with mechanical sterilization, silver-loaded nanocoatings and silver nanocoatings, stimuli-responsive nanomaterials with alternative antibacterial mechanisms and targeted nanodelivery system.[36–48] The current research landscape is characterized by a significant focus on nano-antimicrobial strategies for cementless arthroplasty, where stimuli-responsive nanomaterials and targeted delivery systems represent key hotspots. We have developed a conceptual framework to organize these therapeutic strategies (Figure 3).

Discussion

Nanotechnology-Based Strategies for the Prevention and Treatment of PJI in Cemented Arthroplasty

Cemented arthroplasty relies primarily on poly(methyl methacrylate) (PMMA) bone cement to achieve immediate implant fixation through cement-mediated fixation at the prosthetic surface.[49] When PJI occurs, pathogenic bacteria colonize the bone cement surface, proliferate, and subsequently develop into biofilm communities.[10] Nanotechnology focuses on developing new therapeutic options centered on bone cements. To combat bacterial antibiotic resistance, one promising strategy is to deliver higher concentrations of antibiotics locally or sustain antibiotic release levels above the minimum inhibitory concentration (MIC). This can be achieved by incorporating nanoparticles into bone cement to

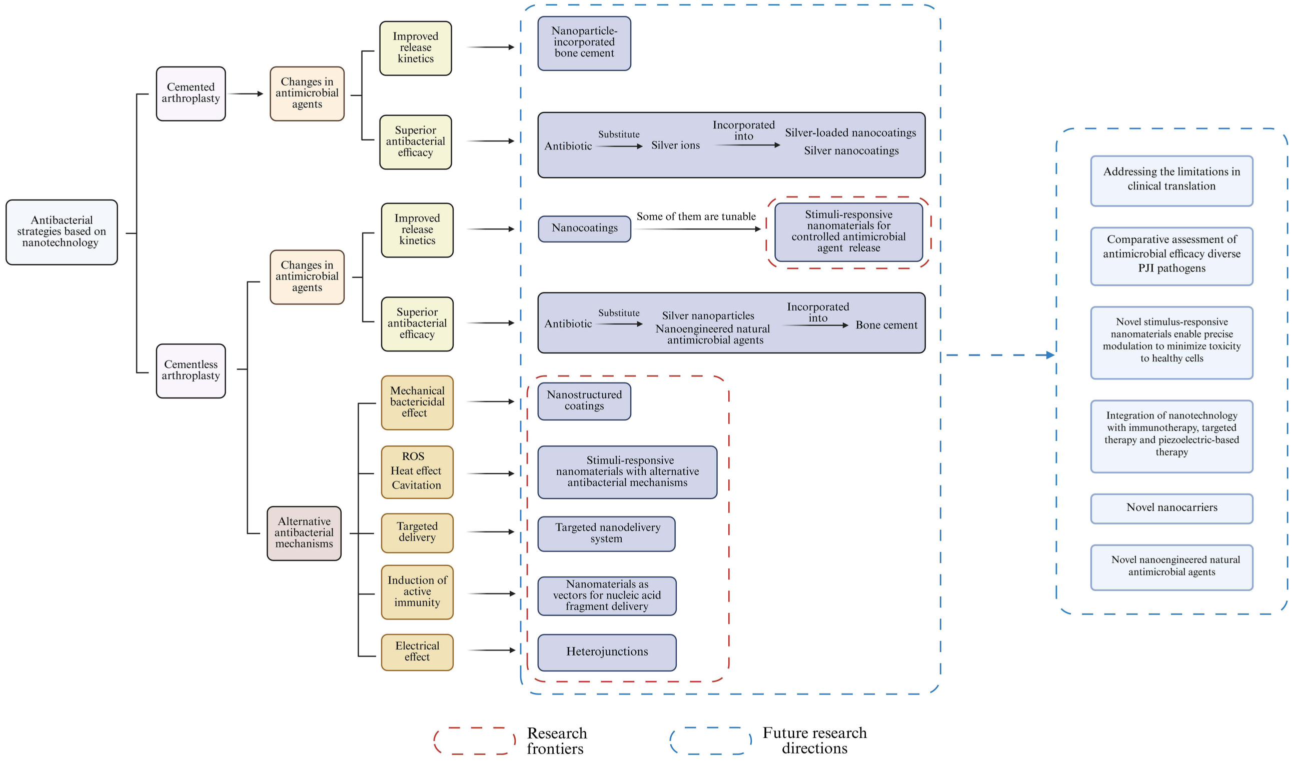


Figure 3 Conceptual framework of current nano-antimicrobial strategies for treating PJI, created in BioRender. Li, (Y) (2025) https://BioRender.com/e4zuqmu.

optimize its antibiotic elution properties. Another strategy involves the use of nanomaterials as antimicrobial agents through nonantibiotic mechanisms. This strategy incorporates antimicrobial metal nanoparticles or natural antimicrobial agents into bone cement, enabling the localized delivery of antimicrobial agents unaffected by existing antibiotic resistance. Table 1 lists nanotechnology-based antimicrobial strategies for treating PJI in cemented arthroplasty.

Nanomaterials for Precise Antibiotic Release Regulation

Limitations of Antibiotic Release from Bone Cement

ALBC is generally considered the standard treatment for PJI in cemented arthroplasty.[56] The optimal performance of ALBC requires the localized delivery of antibiotics at consistently high concentrations. Clinically, ALBC exhibits significant fluctuations in antibiotic release kinetics, characterized by an initial burst release followed by a sustained decline to subtherapeutic concentrations below the MIC.[20,57] This phenomenon may be attributed to the heterogeneous distribution of antibiotics within the bone cement, where antibiotics exist as agglomerates (constituting only a minor fraction of the total antibiotic content). These large antibiotic aggregates create macropores within the cement matrix. Initially, rapid fluid penetration through these macropores facilitates dissolution of readily accessible antibiotics, leading to initial burst release. Subsequently, fluid permeation occurs more slowly through microcracks and smaller voids, gradually dissolving the majority of antibiotics embedded deeper within the cement, resulting in sustained low-level release.[50] Most antibiotics are deeply embedded in the cement matrix where water cannot penetrate and dissolve them, resulting in substantial antibiotic retention, and the free-radical polymerization process further causes drug inactivation, ultimately leading to less than 20% total antibiotic release from the bone cement.[26,31,58,59] The clinical consequence of this limited antibiotic release from bone cement is the creation of a sustained low-concentration antibiotic environment that preferentially selects for highly resistant bacterial strains, provides favorable conditions for their proliferation, and ultimately leads to the gradual dominance of antibiotic-resistant bacteria.[20,60]

Furthermore, the proportion of antibiotics incorporated into bone cement significantly influences their local release concentration.[61,62] However, it is crucial to note that this addition can concurrently compromise the cement's curing process.[61] The mechanical properties of bone cement deteriorate with increasing antibiotic content.[15,20,61] Consequently,

Table 1 Summary of Nanotechnology-Based Antimicrobial Strategies for PJI in Cemented Arthroplasty

Nanomaterials	**Antimicrobial Agents**	**Antimicrobial Agents Efficacy**			**Main Findings**	**Study Type**	**Ref.**
		Evaluation Criteria	**Experimental Group**	**Control Group**			
Silica NPs[a]	CHX[l]	Duration of antimicrobial activity (days)	22	18	The incorporation of SiO_2 NPs loaded with CHX via LbL assembly into bone cement enhanced the release of CHX	In vitro	[22]
Silica NPs	GEN[m] and CHX	Contamination area (μm^2) ($\times 10^5$)	0.5-1	12-13.5	SiO_2 NPs loaded via LbL assembly promoted the release of GEN and CHX from bone cement	In vivo	[27]
CNTs[b]	GEN	Zone of inhibition (mm)	33	26	CNTs in the bone cement promoted the release of GEN	In vitro	[26]
Silica NPs	GEN	Duration of antimicrobial activity (days)	16-19	9-10	SiO_2 NPs as carriers prolonged GEN release from the bone cement	In vitro	[29]
AgNPs[c]	AgNPs	OD_{570}	0.7	0.15–0.25	Bone cement incorporating AgNPs inhibited biofilm formation	In vitro	[32]
CURNs[d]	Curcumin	Inflammatory index score	1.4	5.6	CURN can reverse the immune imbalance in PJI[o]	In vivo	[34]
CS[e] and QCS[f] Nanoparticles	CS and QCS	Log(CFU[n]/mL^2)	2.7–4.5	6-6.3	CS NPs enhanced the bactericidal effect of GEN-loaded bone cement.	In vitro	[35]
Liposomes	GEN	-	-	-	The homogeneous dispersion of liposomes in the bone cement promoted GEN release.	In vitro	[50]
Silica nanoparticles	GEN	Duration of antimicrobial activity (days)	23-25	12-19	Enhanced GEN release from bone cement via incorporation of LbL-assembled SiO_2 NPs	In vitro	[51]
MSNs[g]	GEN	OD_{600}	45-55	97-99	MSNs enhanced the release of GEN from bone cement by providing nanochannels	In vitro	[52]
AgNPs	AgNPs	McFarland standard value	1.20–1.24	> 4	Nano-silver bone cement had superior antibacterial efficacy to ALBC.	In vitro	[53]
Nano Ag-ZrP[h]	Nano Ag-ZrP	Colony count ($\times 10^4$CFU/mL)	205-227	33-39	Nano Ag-ZrP bone cement showed significant antibacterial activity with an optimal content of 1.5–2.0% (w/w)	In vitro	[54]
PMMA[i]/PEO[j] NFs[k] loaded with Lanasol	Lanasol	Bacterial viability	10^4	10^7	Lanasol exhibited good antibacterial activity, which was enhanced after incorporation into PMMA/PEO NFs	In vitro	[55]

Notes: All studies listed aimed to achieve localized delivery of antibiotics, silver ions or natural compounds with controlled kinetics.

Abbreviations: [a]NPs, nanoparticles; [b]CNTs, carbon nanotubes; [c]AgNPs, silver nanoparticles; [d]CURNs, curcumin nanoparticles; [e]CS, chitosan; [f]QCS, quaternary ammonium chitosan derivatives; [g]MSNs, mesoporous silica nanoparticles; [h]ZrP, zirconium phosphate; [i]PMMA, poly (methyl methacrylate) [j]PEO, polyethylene oxide; [k]NFs, nanofibers; [l]GEN, gentamicin; [m]CHX, chlorhexidine; [n]CFU, colony forming unit; [o]PJI, prosthetic joint infection.

antibiotics can only be incorporated at a suitable proportion to ensure that the reduction in mechanical strength remains within an acceptable range. The limited antibiotic loading capacity of bone cement cannot guarantee a sufficient local concentration for complete bacterial eradication. Even if an initially effective concentration is achieved, with the enhancement of bacterial resistance, limited by the impact of antibiotics on mechanical properties, there will always be an upper limit to the antibacterial intensity achievable by bone cement.

ALBC Incorporated with Nanomaterials

Nanomaterial-based drug delivery systems effectively mitigate the limitations of antibiotic release kinetics in conventional bone cement. In these systems, nanoparticles act as carriers that are loaded with antibiotics through encapsulation, adsorption, or layer-by-layer (LbL) deposition, thereby enabling modulation of the release kinetics. By incorporating antibiotic-loaded nanoparticles into bone cement, the nanocomposites maintain mechanical strength within an acceptable range and optimize antibiotic release behavior, resulting in prolonged sustained release profiles along with increased antibiotic release concentrations.[28,63] Moreover, nanoparticles can mitigate the detrimental effects of the bone cement polymerization process on antibiotic stability.[56]

Currently, most studies employ LbL deposition techniques for nanoparticle loading. Multilayer nanoscale coatings can be reproducibly formed on nanomaterials through the alternating deposition of oppositely charged polyelectrolytes.[20,51,64] The nanomaterials are subsequently incorporated into bone cement to form a nanocomposite, enabling sustained local antibiotic release that consistently exceeds the MIC while ensuring complete drug elution. Because antibiotics are pre-encapsulated within the LbL coating interlayer of nanoparticles before being mixed with bone cement, this approach prevents antibiotics from becoming deeply embedded in the cement matrix, where their release would be hindered while simultaneously protecting their bioactivity from damage caused by free-radical polymerization during cement curing.[29,60] Concurrently, antibiotic release occurs either through diffusion across the LbL coating or following coating dissolution, with subsequent diffusion through the bone cement.[27] The former process proceeds more slowly, serving as the rate-limiting step for the entire diffusion system.[29,64] During this process, antibiotics are released slowly and completely, resulting in consistently maintained high concentrations over time (Figure 4a). By adjusting either the coating thickness or its degradation rate, the antibiotic release rate and duration can be moderately modulated.[64] Thaher et al immobilized chlorhexidine onto SiO_2 nanoparticles via LbL assembly, followed by incorporation of the modified nanoparticles into bone cement. In an in vitro setting, the SiO_2-doped cement significantly increased and sustained the release of chlorhexidine compared with the control cement.[22] In a different approach, studies have demonstrated that hollow nanostructures, including carbon nanotubes (CNTs) and mesoporous silica nanoparticles, can form interconnected nanochannel networks through particle–particle contacts within the bone cement matrix.[30,51] The nanochannel network within the bone cement enables complete antibiotic elution to the cement surface while modulating release kinetics through nanoscale pore confinement, ensuring sustained and stable antibiotic delivery. To exploit this property of CNTs, Thaher et al incorporated them into PMMA bone cement. Their in vitro results demonstrated that the incorporation of 3% CNTs into gentamicin-loaded cement resulted in a cumulative release of 45% of the antibiotic over 25 days compared to only 15% from an unmodified commercial gentamicin-loaded cement.[26] An in vitro study by Letchmanan et al demonstrated that incorporating mesoporous silica nanoparticles into PMMA bone cement significantly enhanced the gentamicin release profile. Following an initial burst release, the nanocomposite maintained sustained high-level antibiotic elution, achieving approximately 5-fold greater cumulative release than the control group by day 60.[52]

Furthermore, in Ayre et al's study, nanoparticles modulated antibiotic release from bone cement by altering the porosity of the cement. They coated nano-sized liposomes with Pluronic surfactant to impart hydrophobic properties before incorporating them into the bone cement. This surface modification promoted uniform dispersion of the liposomes, resulting in a composite material with smaller and more homogeneously distributed voids compared to conventional cement. The refined microstructure increases the water-contact surface area and facilitates homogeneous water diffusion from the surface throughout the material, thereby achieving stable and sustained antibiotic release (Figure 4b).[50,65,66] Their in vitro results demonstrated that the cumulative release of gentamicin sulfate from the experimental group of this novel nanocomposite was 2 to 3 times higher than that of the control group.[50]

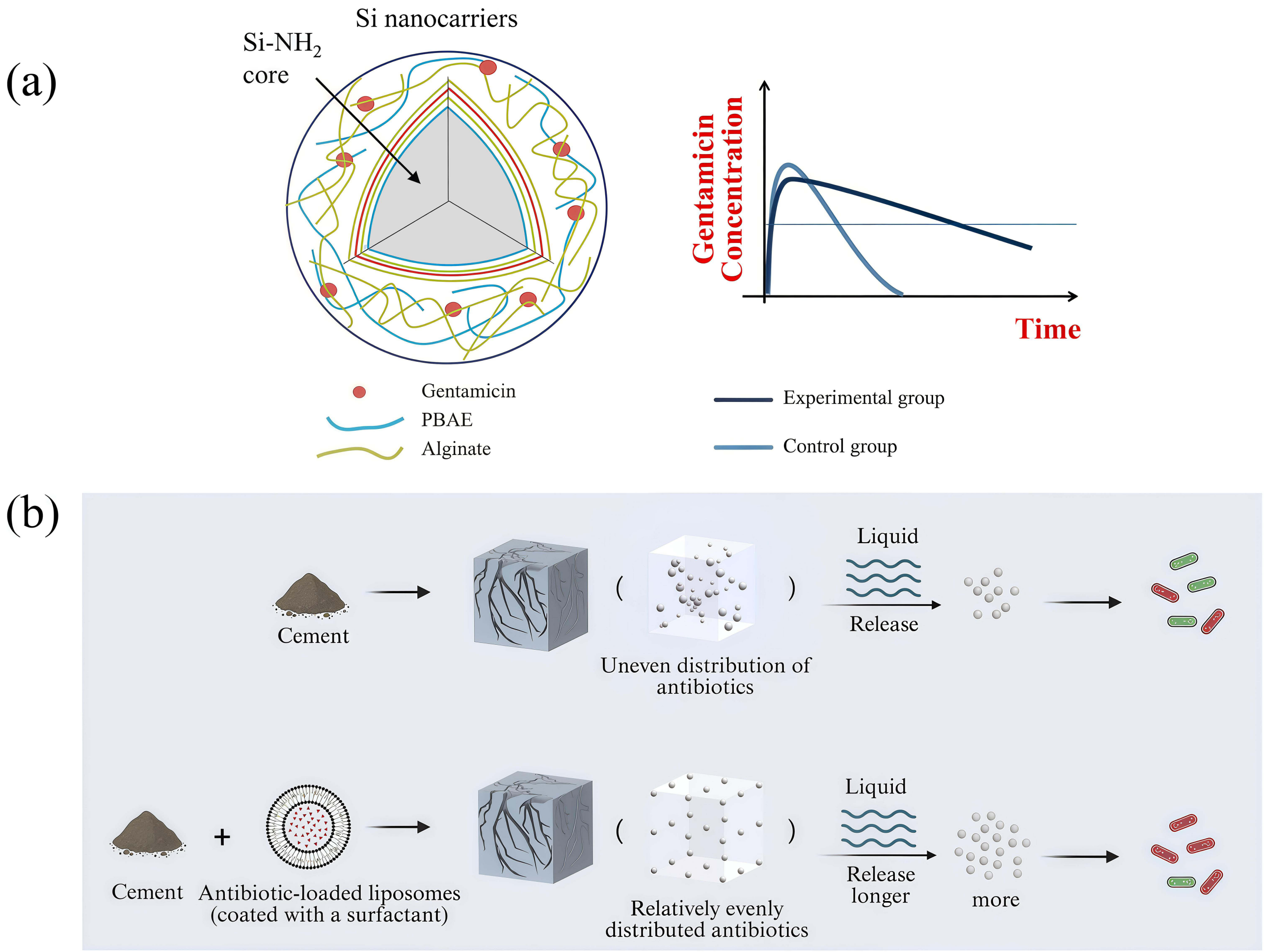


Figure 4 Mechanisms and therapeutic effects of nanomaterial-regulated antibiotic release in bone cement: (**a**) Gentamicin-loaded silicon nanoparticles with LbL coating demonstrated significantly prolonged release of higher antibiotic concentrations compared to conventional antibiotic-impregnated bone cement. Reproduced with permission.[29] (**b**) Nano-sized liposomes regulate antibiotic release kinetics from bone cement by optimizing the spatial distribution of antibiotics throughout the cement matrix, created in BioRender. Li, (Y) (2025) https://BioRender.com/l24a031.

Nanomaterials Used as Antimicrobial Agents

Silver Nanoparticles (AgNPs)

Currently, numerous studies have directly employed nanometallic particles, primarily AgNPs, as antimicrobial agents to combat PJIs in arthroplasty. Therefore, there is a main focus on the application of AgNPs. Recent advances in AgNP applications have effectively addressed traditional cytotoxicity concerns while maintaining antimicrobial efficacy, achieved through their high surface area-to-volume ratio and ultrathin coating technologies that collectively ensure optimal biocompatibility.[32,48,67] Silver ions released from AgNPs through ionization and dissolution in fluids exert broad-spectrum antimicrobial effects by damaging cellular membranes and walls, impairing respiratory chain function, disrupting metabolic pathways, and interfering with genetic material.[17,59,68,69] This multipathway and multitarget antimicrobial mechanism not only effectively eliminates antibiotic-resistant bacteria but also substantially reduces the likelihood of bacterial resistance to silver ion-mediated sterilization.[70]

In cemented arthroplasty, AgNPs are typically directly incorporated into the bone cement.[32,53,71] AgNPs are dispersed in the bone cement matrix with high surface activity and simultaneously increase cement porosity to facilitate water penetration, thereby enabling silver ion release, which achieves effective antibacterial efficacy at low concentrations and reduces systemic toxicity. Wekwejt et al evaluated the antibacterial activity of bone cement incorporated with AgNPs. Their in vitro results indicated that cement modified with 1.5% (w/w) AgNPs could suppress the quantity of Staphylococcus aureus to less than one-third of the level in the control group after 6 hours of exposure.[53] Similarly, in vitro experiments conducted by Chen et al also demonstrated the antibacterial efficacy of silver nanoparticles. The bone cement composite incorporated with 1.5% (w/w) nano-silver-loaded zirconium phosphate achieved inhibition rates of 83.23% against Streptococcus mutans and 64.00% against Escherichia coli.[54]

Nanoengineered Natural Antimicrobial Agents

With the emergence of bacterial resistance due to the prolonged use of ALBC, natural antimicrobial agents have become viable alternative solutions. Nanotechnology effectively addresses the application limitations of natural antimicrobial agents while utilizing high surface area-to-volume ratios of nanoparticles to significantly enhance antibacterial activity.[33–35] The study by Andersson et al involved incorporating the natural antimicrobial agent Lanasol into a blend of PMMA and polyethylene oxide (PEO), which was subsequently processed into nanofibers via electrospinning to investigate its antibacterial properties. In vitro assays demonstrated that fibers containing 4 wt% Lanasol reduced Staphylococcus aureus viability by approximately 1000-fold compared to the control group.[72] Shi et al developed chitosan nanoparticles and their quaternary ammonium derivatives for bone cement incorporation, effectively preventing the decrease in mechanical properties caused by direct chitosan blending.[35] To address the poor aqueous bioactivity of curcumin, Peng et al developed curcumin nanoparticles (CURNs), which not only increased water solubility but also demonstrated significant efficacy against Staphylococcus aureus infections in vivo.[34]

Furthermore, several antibacterial strategies utilizing nanoengineered natural antimicrobial agents for the treatment of oral diseases provide valuable insights and references. In vitro experiments conducted by Nageeb et al demonstrated that neem nanoparticles exhibit enhanced antibacterial efficacy compared to non-nanoengineered neem extracts. This suggests that nanotechnology enables neem to achieve sufficient antimicrobial activity at lower doses, thereby exhibiting lower toxicity.[55] The development of nanoparticle-based formulations of natural antibacterial agents—such as aloe-emodin, quercetin, tannic acid, and gallic acid, which have demonstrated effective antimicrobial properties when incorporated into bone cement—represents a promising research direction for enhancing their efficacy and reducing potential toxic side effects.[73,74]

Nanotechnology-Based Strategies for the Prevention and Treatment of PJI in Cementless Arthroplasty

Cementless arthroplasty avoids cement-related complications, including inflammatory reactions, third body wear, and osteolysis, by achieving durable biological fixation through direct bone ingrowth into the implant's porous surface coating.[20,75–77] However, postoperative porous implant-coated surfaces can be adhered to by bacteria, potentially leading to PJI.[78] Current research prioritizes nanotechnology-based surface modifications to develop nanocoatings capable of sustained local delivery of high-concentration antibiotics or alternative antimicrobial mechanisms independent of traditional antibiotics. Table 2 lists nanotechnology-based antimicrobial strategies for PJI in cementless arthroplasty.

Nanocoatings and Nanomaterials for Precision Antimicrobial Agent Release Regulation

Antibiotic-Loaded Nanocoatings

To mitigate the risk of PJI, antibiotic-loaded nanocoatings can be engineered onto the implant surface to achieve prolonged local delivery that sustains antibiotic concentrations above the MIC while simultaneously inhibiting bacterial adhesion and biofilm formation. Suchý et al developed a nanostructured collagen/hydroxyapatite composite layer by electrospinning, followed by vancomycin loading via impregnation (electrospun-impregnated samples). In contrast to lyophilized collagen/hydroxyapatite/vancomycin microstructured layers (lyophilized samples), the electrospun-impregnated samples presented significantly higher antibiotic release rates in this in vitro study, with vancomycin concentrations in human plasma remaining above the MIC for over 4 weeks.[42] In the study of Della Fara et al, TiO2 nanotubular layers were first fabricated on Ti alloy surfaces via anodic oxidation, followed by gentamicin loading via electrophoretic deposition (EPD). In an in vitro phosphate-buffered solution (pH=7.4), the system demonstrated only a 10% initial burst release of gentamicin within the first 78 minutes, with subsequent sustained release over 3 days.[79]

Furthermore, given the increasing bacterial resistance, merely increasing the local antibiotic release dosage is not a sustainable solution. Consequently, some studies have explored antimicrobial peptides (AMPs) as potential alternatives

Table 2 Summary of Nanotechnology-Based Antimicrobial Strategies for PJI in Cementless Arthroplasty

Nanomaterials	Antimicrobial Agents	Antimicrobial Agents Efficacy			Main Findings	Study Type	Ref.
		Evaluation Criteria	Experimental Group	Control Group			
PCL^{Col}/PVA$^{HA\ a)}$	Doxy$^{k)}$	Bacteria OD (day 7)	0.18–0.2	0.4–0.45	PCL^{Col}/PVA^{HA} NFs enabled sustained Doxy release, resulting in effective antibacterial action	In vitro	[23]
Hydroxyapatite NPs$^{b)}$	VAN$^{l)}$-HCl	CFU$^{s)}$/mL	1.4×10^{4}	1×10^{4}	VAN-nHAP/OSA/GT$^{t)}$ enables sustained release of sufficient VAN for effective antibacterial activity	In vitro	[31]
Titanium carbide nanosheet	-	Bacterial viability (%)	5-10	95-99	C-T@Ti$_3$C$_2$$^{u)}$ achieves sterilization and promotes osteogenesis through sonodynamic and chemodynamic effects	In vitro and in vivo	[38]
IRPNPs$^{c)}$	RIF$^{m)}$ and ICG$^{n)}$	Log10((CFU+1)/mL)	1.2–1.4	4.3–4.5	IRPNPs synergistically sterilize through combined photothermal effect and antibiotic release	In vitro	[39]
CaO2 NPs	-	Antibacterial efficiency (%)	99	70	The newly developed nano-painting releases ROS$^{v)}$ under acidic conditions	In vivo	[40]
Ag/BSA NPs$^{d)}$	Ag/BSA NPs	OD$_{630}$	0.4	0.03–0.05	Ag/BSA NPs immobilized on PHBV film exhibit acid-triggered release	In vitro	[41]
Collagen/hydroxyapatite nanocoatings	VAN	Zone of inhibition (mm)	18-19	18	VAN-impregnated collagen/hydroxyapatite nanocoatings delivered sufficient antibiotics locally	In vitro	[42]
CICNT$^{e)}$	-	Average cell count (cell number/mm2)	60-85	20-25	CICNT significantly reduced surface biofilm formation	In vitro	[43]
TiO$_2$ nanostructured coatings	-	CFU/sample (day 20)	1010	108-109	Spike-like TiO$_2$ nanostructured coatings suppress bacterial colonization	In vitro	[44]
AgNPs	AgNPs	CFU/mL	10^{9}-10^{10}	10^{8}	Fractal silver dendrites demonstrate potent antibacterial efficacy	In vitro	[45]
PHBV$^{f)}$ nanofibers	AgNPs	Growth inhibition (%)	10	95-100	Ag-containing PHBV nanofibers demonstrate excellent antibacterial activity	In vitro	[48]
Ag nanolayer	Ag ions	OD$_{595}$	1.05	0.4	The Ag nanolayer coated on the implant surface by ALD$^{w)}$ provides sufficient antibacterial efficacy with low cytotoxicity	In vitro and in vivo	[67]
TiO$_2$ nanostructured coatings	GEN$^{o)}$	CFU/mL	2×10^{6}	4.5×10^{8}	GEN-loaded TiO$_2$ nanotubes exhibited favorable antibiotic elution and effective bacteriostasis	In vitro	[79]
MSN$^{g)}$	AMP$^{p)}$	CFUq)/mL	4.3×10^{6}	0.1×10^{6}	AMP-loaded MSNs are effective in eradicating bacteria and promoting osteogenesis	In vivo	[80]
MSN	AMP and OFL$^{q)}$	CFU/mL	0	$0.8–1.2\times10^{8}$	The co-assembled MSNs with AMP and OFL exhibited a synergistic antibacterial effect in response to both heating and pathogen stimulation	In vivo	[81]
ZIF8	AMP LL37	CFU/mL	15-20	850-950	LL37@ZIF8-LL37$^{x)}$ directly eradicating S. aureus while simultaneously reversing the immunosuppressive state	In vivo	[82]
GLM-Fe$^{h)}$	-	Inactivated cells (%)	15-25	90-99	Under a magnetic field, GLM-Fe achieves bacterial killing and biofilm disruption	In vitro	[83]
C-TiO$_2$ NR	-	Antibacterial efficiency (%)	85	0	C-TiO2 NR$^{y)}$ exhibits sufficient photothermal antibacterial activity and osteogenic capacity	In vivo	[84]
AgNPs and ZnO NPs	AgNPs and ZnO NPs	Antibacterial efficiency (%)	70-80	0-5	ZnO NP addition yields antibacterial synergy with AgNPs and reduced Ag+ ion toxicity	In vitro and in vivo	[85]
PDA$^{i)}$-AgNP coating	AgNPs	Biofilm concentration Log$_{10}$(CFU/mL)	3.5-4	7.5-8	The 3D scaffold coated with a PDA-AgNP layer exhibits dual functionality: antibacterial and enhanced osteogenesis	In vitro	[86]
AH-Sr-AgNPs$^{j)}$	AgNPs	CFU/dish	1-2	260-280	AH-Sr-AgNPs provide Ag^{+} release for antibacterial activity while releasing Sr^{2+} to promote osteogenesis	In vitro and in vivo	[87]
MoS$_2$ nanosheets	HNTM$^{r)}$	CFU/mL	5.35×10^{7}	3.47×10^{9}	HNTM-MoS$_2$ enables ultrasound-triggered sterilization via the piezoelectric effect	In vivo	[88]
Sulfide nanosheets	-	Bacterial activity (%)	0	98-100	BGS/MCFS$^{z)}$ possesses dual functions of photothermal sterilization and osteogenic promotion	In vivo	[89]

Notes: Antibacterial mechanism of references 23, 31, 42, 79, 82, 83, 84 based on precise and controlled antibiotic release. Antibacterial mechanism of references 45, 48, 64, 113, 120, 121 based on local delivery of silver, zinc, or strontium ions. Antibacterial mechanism of references 40, 41 based on sterilization via stimulation-responsive release of antibacterial agents. Antibacterial mechanism of references 43, 44, 97 based on sterilization via mechanical mechanisms. Antibacterial mechanism of references 38, 39, 112, 127, 128 based on sterilization via stimulation-responsive physical mechanisms.

Abbreviations: $^{a)}$PCL^{Col}/PVA^{HA}, coaxial electrospun polycaprolactone/polyvinyl alcohol core-sheath nanofiber blended with both hydroxyapatite nanorods and type I collagen; $^{b)}$NPs, nanoparticles; $^{c)}$IRPNPs, indocyanine green and rifampicin co-loaded poly(lactic-co-glycolic acid) nanoparticles; $^{d)}$Ag/BSA NPs, bovine serum albumin capped silver nanoparticles; $^{e)}$CICNT, carbon-infiltrated carbon nanotubes; $^{f)}$PHBV, poly(3-hydroxybutyrate-co-3-hydroxyvalerate); $^{g)}$MSN, mesoporous silica nanoparticle; $^{h)}$GLM-Fe, Magnetic Galinstan-based liquid-metal microparticles and nanoparticles; $^{i)}$PDA, polydopamine; $^{j)}$AH-Sr-AgNPs, a Sr2+/Ag+ delivery system constructed on the Ti surface via an alkali-heat treatment; $^{k)}$Doxy, doxycycline; $^{l)}$VAN, vancomycin; $^{m)}$RIF, rifampicin; $^{n)}$ICG, indocyanine green; $^{o)}$GEN, gentamicin; $^{p)}$AMP, antimicrobial peptide; $^{q)}$OFL, ofloxacin; $^{r)}$HNTM, porphyrin-based hollow metal-organic framework; $^{s)}$CFU, colony forming unit; $^{t)}$VAN-nHAP/OSA/GT, a mixture of vancomycin-loaded nano-hydroxyapatite with oxidized sodium alginate and gelatin; $^{u)}$C-T@Ti3C2, CaO2-loaded 2D titanium carbide nanosheets; $^{v)}$ROS, reactive oxygen species; $^{w)}$ALD, atomic layer deposition; $^{x)}$LL37@ZIF8-LL37, dual-functional LL-37-encapsulated/-modified porous ZIF-8 nanomaterial; $^{y)}$C-TiO2 NR, carbon dots-doped TiO2 nanorod array; $^{z)}$BGS/MCFS, bioactive glass scaffold functionalized with metal sulfide nanosheets.

to antibiotics for localized antibacterial applications. Owing to the inherent instability and rapid degradation of AMPs in vivo, resulting in an extremely short antibacterial duration, nanocoatings need to be constructed on implant surfaces as carriers to anchor AMPs for achieving controlled delivery.[90,91] Dong et al developed a functionalized titanium implant, Ti-M@A. The researchers employed diselenide-bridged mesoporous silica as a carrier to anchor the antimicrobial peptide HHC36 via selenium-assisted functionalization. In vivo experiments demonstrated that the Ti-M@A group achieved a 98.82% eradication rate against S. aureus after 7 days.[80] Moreover, under certain conditions, AMPs and antibiotics can be coincorporated into a nanodrug delivery system to exert synergistic antimicrobial effects. This was confirmed by Yu et al's in vivo studies, with their codelivery platform for antimicrobial AMPs and antibiotics exhibiting significantly enhanced biofilm eradication efficacy compared with single-agent delivery systems.[81] In recent years, by utilizing the immunomodulatory properties of AMPs, AMP-based nanodelivery systems have also achieved new progress in immunotherapy applications. Qu et al encapsulated the antimicrobial peptide LL37 plasmid using porous ZIF8 nanomaterials and then performed surface modifications to construct LL37@ZIF8-LL37 nanoparticles with gene transfection capability. This nanoplatform enables sustained LL37 production in surrounding cells via plasmid transfection, which modulates myeloid-derived suppressor cells (MDSCs) to counteract local immunosuppression. In vivo experiments confirmed the efficacy of this antibacterial strategy.[82]

Stimuli-Responsive Nanomaterials for Controlled Antimicrobial Agent Release

The theoretical foundation of stimuli-responsive nanomaterials has been relatively well established, and a number of studies have begun exploring their applications in the context of PJI. Recent research has demonstrated that the development of stimuli-responsive nanomaterials successfully overcomes the limitations of conventional nanoparticles, as these advanced materials can precisely deliver drugs or directly exert antimicrobial effects in response to endogenous or exogenous stimuli while enabling accurate artificial control of antimicrobial activity (Figure 5a).[92,93] During localized bacterial infections, microenvironmental changes in pH, redox products, enzymes, and toxins serve as endogenous stimuli that typically induce various nanomaterial responses, including protonation, chemical bond cleavage, charge reversal, matrix metalloproteinase (MMP) activation, or disulfiram-like reactions, consequently triggering the release of antimicrobial agents from the coating.[92,94,95] These infection-responsive nanomaterials, which release antibiotics upon bacterial stimulation, have significant potential for preventing PJI. Bakare et al developed a pH-responsive antimicrobial system by electrostatically adsorbing bovine serum albumin-capped silver nanoparticles (Ag/BSA NPs) onto poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) nanofibrous scaffolds. During in vitro testing, bacterial growth-induced accumulation of acidic metabolites decreased the local pH, subsequently weakening electrostatic interactions and triggering the release of Ag/BSA nanoparticles. This pH-dependent release mechanism demonstrated significant antibacterial efficacy against both gram-negative and gram-positive bacteria (Figure 5b).[41] Zhang et al developed pH-responsive nanomaterials whose acid-triggered disassembly enables a Fenton-like reaction that produces hydroxyl radicals (•OH), demonstrating potent antibacterial activity in vivo (Figure 5c).[40] Furthermore, certain stimuli-responsive nanomaterials can be activated by exogenous stimuli to release antimicrobial agents. Research on these materials for PJI prevention and treatment remains scarce.

Nanocoatings and Nanomaterials with Alternative Antibacterial Mechanisms

Nanostructured Coatings with Mechanical Sterilization

Certain natural biological surfaces, particularly the wings of cicadas and dragonflies, exhibit inherent antimicrobial properties. By mimicking the natural nanostructures found on biological surfaces, researchers have engineered biomimetic nanomaterial surfaces whose mechanobactericidal effects directly reduce bacterial adhesion, leading to suppressed biofilm formation and bacterial eradication.[43] Bioinspired nanostructured surfaces primarily achieve bactericidal effects through direct-contact mechanical disruption of cell membranes, thereby avoiding being limited by antibiotic resistance development while demonstrating minimal cytotoxicity.[96–98] These nanostructured surfaces employ two distinct mechanical bactericidal mechanisms: (1) The sharp-edged nanostructures mechanically disrupt bacterial membranes through direct physical cutting and concurrent lipid extraction, resulting in pore formation, osmotic imbalance, and ultimately cell death (Figure 6a).[99] (2) Nanopillar structures cause bacterial membrane rupture by inducing tensile deformation that

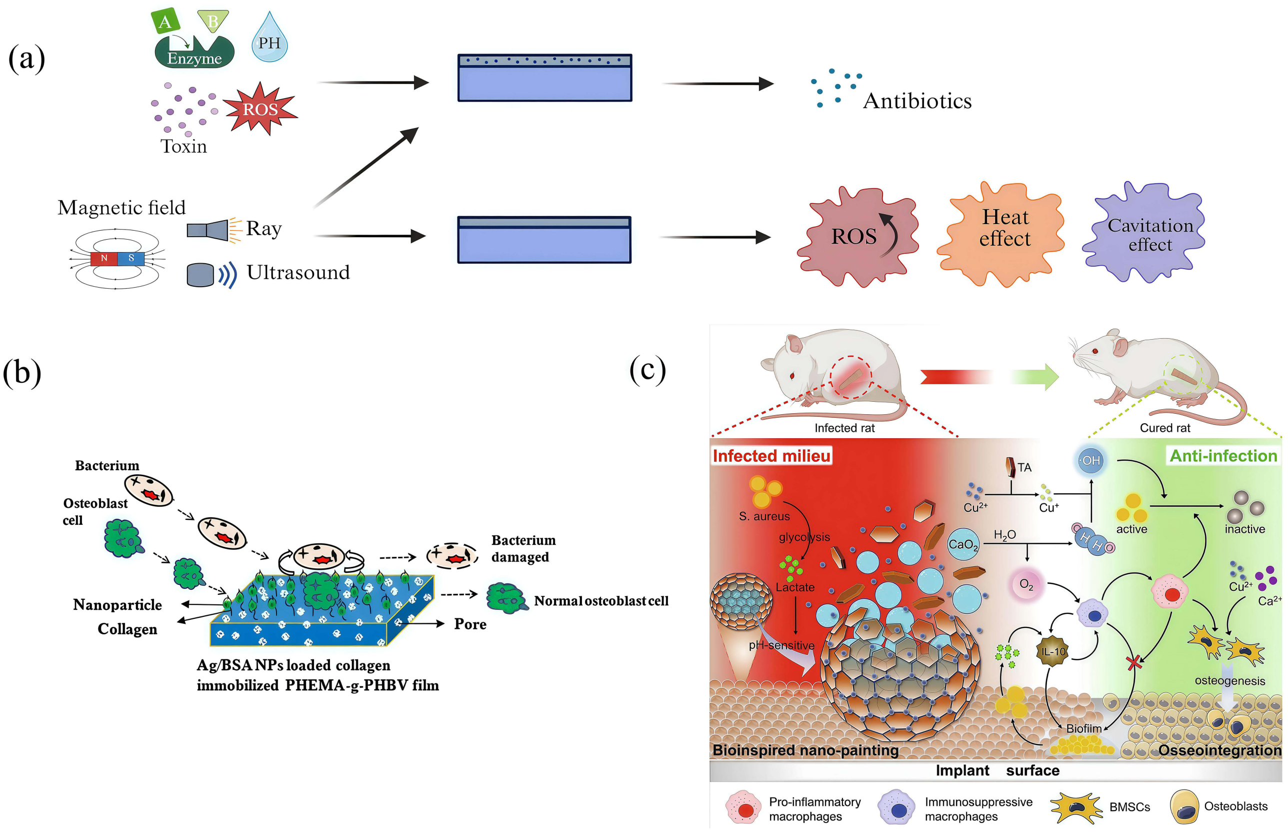


Figure 5 Mechanisms and applications of stimuli-responsive antimicrobial nanomaterials: (**a**) Stimuli-responsive nanomaterials trigger targeted effects in response to endogenous or exogenous stimuli, created in BioRender. Li, (Y) (2025) https://BioRender.com/g654468. (**b**) Ag/BSA nanoparticles pH-dependently release antimicrobial agents to eradicate adherent bacteria on surface. Reproduced with permission.[41] (**c**) Bioinspired nano-painting decomposes under acidic conditions to catalytically generate •OH, exhibiting potent antibacterial effects against surface-adherent bacteria. Reproduced with permission.[40]

exceeds the elastic limit of the membrane (Figure 6b and c).[96,99–101] In addition, bioinspired nanostructured surfaces can also exhibit antimicrobial effects through other mechanisms: (1) Nanotopography participates in immune regulation by modulating macrophage polarization and mediating neutrophil aggregation.[102] (2) Sharp nanostructures modulate bacterial antibiotic susceptibility by inducing oxidative stress and physically disrupting cell wall integrity.[103]

Numerous studies have demonstrated the potent antibacterial efficacy of this nanostructured surface. Through hydrothermal etching, Bright et al engineered TiO2 surfaces featuring spike-like nanostructures on Ti alloy substrates, with experimental results confirming a substantial reduction in both Staphylococcus aureus and Pseudomonas aeruginosa in vitro.[44] Compared with controls, Morco et al engineered carbon-infiltrated CNT coatings with nanopillar arrays on both silicon wafers and stainless steel, which resulted in significantly reduced MRSA adhesion under in vitro conditions.[43] Elbourne et al integrated this mechanobactericidal strategy with stimuli-responsive nanomaterials by developing magnetic Galinstan-based liquid-metal nanoparticles (GLM-Fe). Upon activation under a rotating magnetic field, these particles undergo morphological transformation to form sharp edges and exhibit rotational motion, leading to the physical disruption of Staphylococcus aureus and Pseudomonas aeruginosa biofilms in vitro, while allowing for precise external control.[83]

The surface nanotopography of implants also results in superior antiadhesion performance compared with that of conventional surfaces.[99,104–108] Under nanoscale roughness, bacteria primarily establish point contacts with surface nanotopography, lacking stable anchoring points, and with weaker bacterium–surface interactions than interbacterial forces, they aggregate into clusters, thereby enhancing immune recognition and elimination.[99,104] Concurrently, these nanostructures facilitate superhydrophobicity through nanoscale air entrapment beneath the liquid interface, achieving the Cassie–Baxter state.[108,109] Bacterial attachment is effectively inhibited by the lack of available anchoring sites resulting

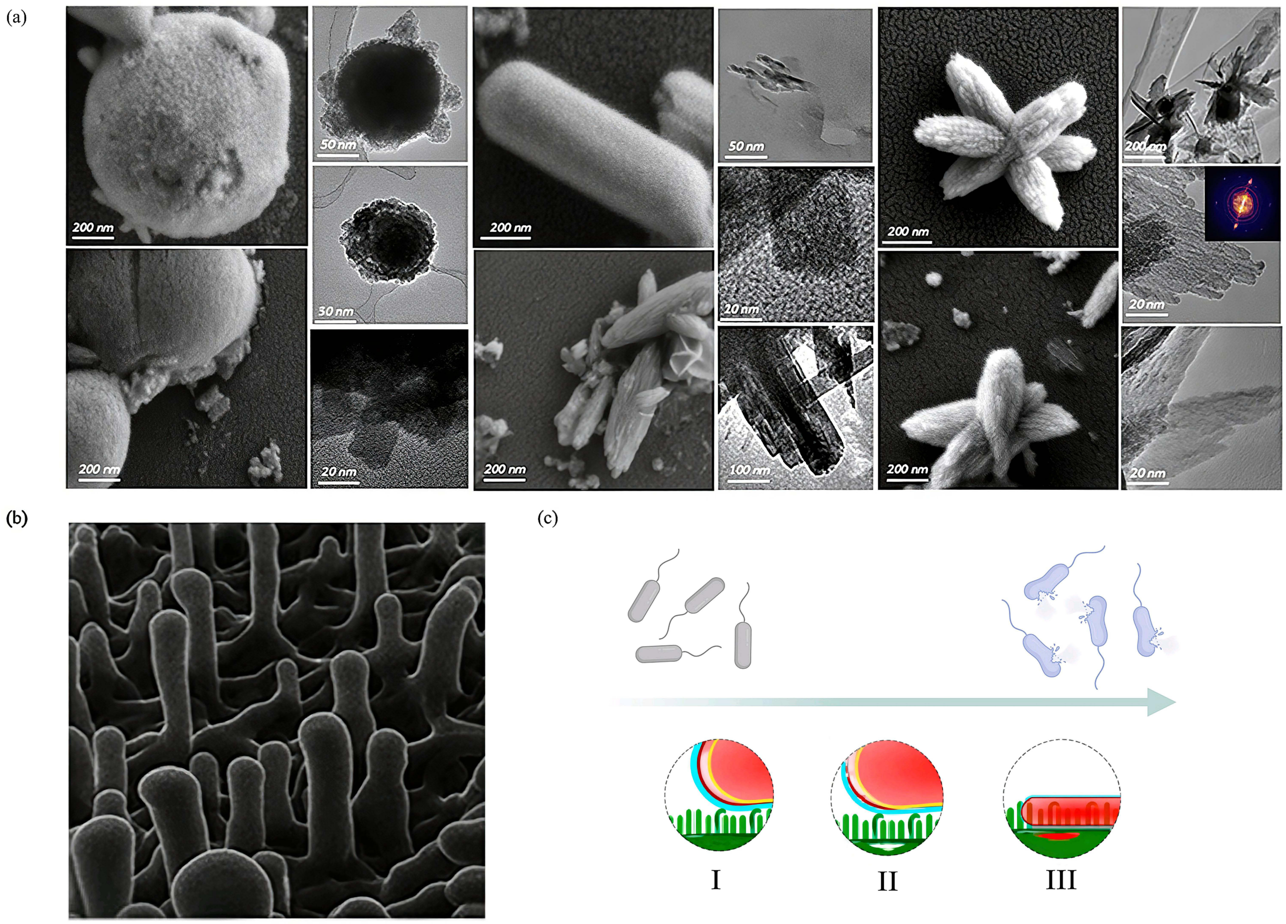


Figure 6 Nanostructured coatings with mechanical sterilization: (**a**) SEM images of metal nanoparticles with sharp edges. Reproduced with permission.[83] (**b**) SEM image of the nanopillar structure. Reproduced with permission.[96] (**c**) Three-step antibacterial process of nanopillars: (**I**) bacterial attachment; (II) movement and membrane penetration by nanopillars; (III) membrane rupture and cell death, created in BioRender. Li, (Y) (2025) https://BioRender.com/4yq1431. Reproduced with permission.[96]

from the entrapped air layer beneath the liquid surface.[104,110] However, research on the applications of purely anti-adhesive nanostructured joint implant surfaces remains limited; as such, surfaces rely mainly on sterilization mechanisms that inherently provide more direct and effective antibacterial action.[43,44,111]

In addition, a "Race for the Surface" phenomenon occurs between host cells and bacterial pathogens on the implant interface. Beyond exerting mechanical antibacterial effects, these nanostructured coatings also modulate the adhesion and subsequent colonization of mesenchymal stem cells (MSCs).[36,112] Due to the scarcity of literature on the effects of sharp-edged nanostructures on MSCs, the discussion herein focuses specifically on the contribution of nanopillar-type structure, including nanopillars, nanoneedles and nanorods. Studies have demonstrated that nanopillar-type structures can effectively promote the adhesion of MSCs to material surfaces through the provision of anchoring sites, upregulation of integrin expression, and induction of focal adhesion formation.[113–115] In vitro experiments conducted by Degli Esposti et al demonstrated that the ACP GS group with a nanostructured needle surface exhibited significantly higher expression of the adhesion markers focal adhesions (FA) and paxillin in MSCs compared to the control group.[113] Furthermore, nanopillar-type structures promoted the proliferation and osteogenic differentiation of MSCs.[113–116] This induction of osteogenic differentiation may be attributed to the mechanical cues provided by the nanostructures.[113] In vitro experiments by Yang et al revealed that TiO_2 nanorod structures can promote the polarization of macrophages from the M1 to the M2 phenotype.[117] Subsequently, the M2 macrophages expressed TGF-β1 and BMP-2, which enhanced the osteogenic differentiation of bone marrow MSCs. Meanwhile, studies by Fiedler et al demonstrated that the osteogenic differentiation of MSCs induced by nanopillar structures is influenced by the height of the nanostructures, as observed in vitro.[113]

However, it should be noted that the nanopillar-induced proliferation of MSCs is independent of specific geometrical details of the nanopillars, including their height, mutual distance, and diameter. Some studies have attempted to leverage this characteristic of nanopillar-like structures to develop multifunctional nanomaterials with both antibacterial and osteogenic properties. For instance, He et al developed a TiO_2 nanorod array incorporated with carbon dots (CDs), which exhibited significant antibacterial efficacy in vivo under near-infrared (NIR) light irradiation, while also effectively promoting the adhesion and proliferation of MSCs.[84]

Silver-Loaded Nanocoatings and Silver Nanocoatings

The application of silver nanoparticles in cementless arthroplasty generally involves two distinct approaches: (1) The incorporation of silver nanoparticles into the biologically active coating on the implant surface provides effective antimicrobial activity while significantly reducing systemic toxicity compared with direct prosthesis coating but essentially does not affect the biological bonding between the porous surface coating and bone.[46,47] In Xing et al's study, electrospun PHBV nanofiber scaffolds with randomly embedded silver nanoparticles were applied as implant surface coatings, which effectively inhibited *Staphylococcus aureus* and *Klebsiella pneumoniae* proliferation in vitro.[48] Zhang et al fabricated a multifunctional coating composed of silver nanoparticles, zinc oxide nanoparticles (ZnO NPs), and hydroxyapatite on titanium alloy substrates via laser cladding. This technique enables the sustained release of silver and zinc ions at therapeutically effective low concentrations over extended periods. Notably, the incorporated zinc ions not only counterbalanced the cytotoxicity of silver ions but also demonstrated synergistic antibacterial effects with silver ions, as conclusively verified by their in vitro and in vivo experimental results.[85] Furthermore, several studies on antimicrobial surfaces for nonarticular implants offer valuable insights for joint implant development. For example, Qian et al fabricated a silver ion-regulating superhydrophobic surface through sequential deposition of polydopamine (PDA) and silver nanoparticles on stainless steel, which demonstrated remarkable synergistic antimicrobial effects between the nanoparticles and the superhydrophobic surface in vitro.[118] (2) Another method involves direct surface deposition of silver nanoparticles onto implant substrates. Owing to the toxicity of silver, atomic layer deposition (ALD) and plasma electrolytic oxidation (PEO) are typically employed to coat silver nanolayers on implant surfaces, ensuring both sufficient antibacterial efficacy and low cytotoxicity through precise control of the coating thickness.[67,119–121] Devlin-Mullin et al applied atomic layer deposition to coat peptide implants with silver nanolayers, which effectively suppressed *Staphylococcus epidermidis* colonization in vitro while substantially reducing systemic silver toxicity.[67] In addition, the antimicrobial efficacy varies significantly among silver nanostructural morphologies, with fractal silver dendritic coatings demonstrating superior antibacterial performance (Figure 7).[45,122,123] Franco et al conducted

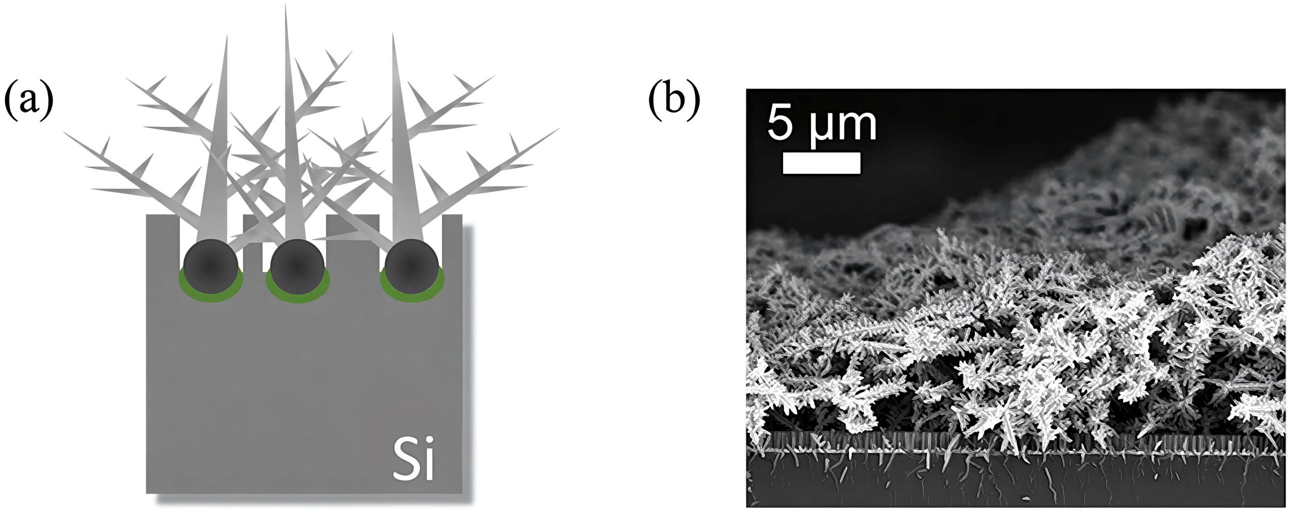


Figure 7 Morphological characteristics of excellent biocompatible fractal silver dendrites: (**a**) Silver dendritic nanostructures grown on silicon substrates. Reproduced with permission.[45] (**b**) SEM image of the cross section of the Ag dendrite sample. Reproduced with permission.[45]

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a comparative study evaluating fractal silver dendritic coatings against other silver-based coatings, and their findings demonstrated that the fractal silver dendritic coatings exhibited significantly enhanced antibacterial activity, as assessed in vitro, while maintaining superior biocompatibility compared with conventional silver coatings.[45]

Recent studies have incorporated AgNPs into 3D-printed porous implant scaffolds by doping or surface coating, with these AgNP-loaded scaffolds demonstrating effective antibacterial properties.[71,121] Some studies have focused on developing dual-functional scaffolds with combined antimicrobial and osteogenic properties. Merlo et al fabricated a 3D porous scaffold coated with a polydopamine layer, followed by the deposition of AgNPs. Their in vitro results demonstrated that the PDA-AgNP coating not only markedly suppressed *Staphylococcus aureus* adhesion and biofilm formation but also synergized with the porous architecture to enhance early-stage osteoblast proliferation and differentiation. This bifunctional coating provided osteoblasts with a competitive advantage over pathogenic bacteria on the implant surface.[86] Li et al developed an AH-Sr-AgNP drug delivery system on 3D-printed implant surfaces. Through the localized release of bioactive ions, the system simultaneously provided antibacterial effects via silver ions while promoting osteogenic activity through Sr ion-mediated M2 macrophage polarization, as demonstrated in vitro.[87]

Stimuli-Responsive Nanomaterials with Alternative Antibacterial Mechanisms

Stimuli-responsive nanomaterials with alternative antibacterial mechanisms primarily function through exogenous stimulus regulation. Exogenous stimuli (eg, light, ultrasound, magnetic fields) activate responsive nanomaterials to generate ROS, thermal effects, or cavitation, directly killing bacteria or triggering antimicrobial drug release.[92,97,124–127] Compared with endogenous stimuli, exogenous stimuli offer human-controllable advantages, enabling the precise adjustment of treatment duration and intensity. These stimulus-responsive nanomaterials are particularly suitable for treatment. Lee et al developed indocyanine green and rifampicin co-loaded poly(lactic-co-glycolic acid) nanoparticles (IRPNPs) to combine antibiotic therapy with photothermal therapy for treating PJI. In vitro testing demonstrated that, compared with individual therapies, near-infrared (NIR)-activated IRPNPs exhibited superior antibacterial efficacy on porous substrates mimicking cementless joint implant coatings.[39] Yu et al synthesized a novel Ti-PDA@SNP-OGP nanocomposite, where NIR irradiation induced the photothermal conversion of PDA nanoparticles, thereby stimulating localized nitric oxide (NO) release. This strategy achieved on-demand NO release at deep PJI sites through precisely controlled intermittent NIR irradiation. In vivo experiments confirmed that NIR-irradiated TiPDA@SNPOGP implants achieved complete eradication of surface biofilms.[128] Feng et al engineered piezoelectric-enhanced nano-sonosensitizers by electrostatically grafting MoS_2 nanosheets onto a porphyrin-based hollow metal-organic framework (HNTM). This design significantly amplified ultrasound-triggered ROS generation from HNTM, achieving remarkable efficacy against MRSA-induced osteomyelitis in vivo (Figure 8).[88] Building on the demonstrated antibacterial efficacy of stimuli-responsive nanomaterials, some studies have attempted to develop dual-function stimuli-responsive nanomaterials with antibacterial and osteogenic capabilities. Yu et al developed CaO_2-loaded 2D titanium carbide nanosheets (C-T@Ti_3C_2) that can not only generate sufficient ROS for antibacterial purposes under ultrasound stimulation but also promote localized calcium ion deposition to increase bone formation, which was confirmed in mice models.[38] The bioactive glass scaffold functionalized with metal sulfide nanosheets (BGS/MCFS) developed by Bian et al has a similar function, responding to photothermal effects while promoting vascularized osteogenesis. In vivo experiments demonstrated that compared with controls, NIR-treated BGS/MCFS not only effectively eradicated periprosthetic infections in PJI models but also promoted bone regeneration, with an 8.5-fold increase in total bone volume in bone defect models.[89]

Emerging Antimicrobial Strategies for Nanotechnology in PJIs

Nanotechnology Combined with Biologically Targeted Therapies

Peptide-modified nanomaterials serve as drug carriers, enabling nanomaterials to act as carriers to be targeted to the infected site and release antibiotics.[129] This approach enables targeted delivery of antibiotics to the infected site, exposing antibiotic-resistant pathogens to extremely high local antibiotic concentrations. It achieves effective eradication of antibiotic-resistant bacteria while substantially mitigating adverse effects of systemic antibiotics. Nie et al developed a bone and bacteria dual-targeted nanocarrier through the functionalization of mesoporous silica nanoparticles (MSNs) with D6 and UBI29-41 peptides. In rat model experiments, the experimental group presented the lowest bacterial counts

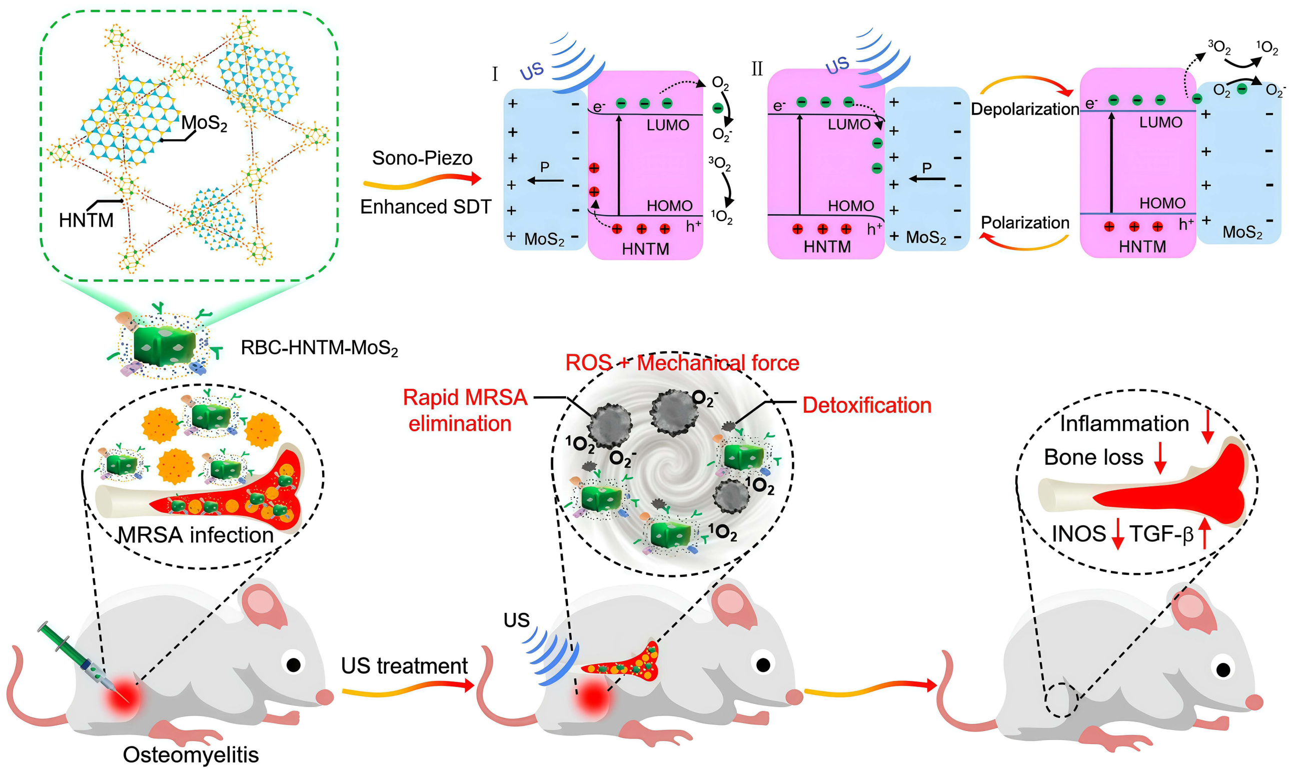

Figure 8 The mechanism of ultrasound-activated HNTM-MoS_2 nanocomposites eliminating MRSA. Reproduced with permission.[88] Panels I and II illustrate two distinct configurations of the MoS2 and HNTM composite: Panel I corresponds to the antibacterial mechanism when MoS2 is coupled at its anode side with HNTM, whereas Panel II shows the scenario involving the cathode side of MoS2.

on implant surfaces and the mildest infection-induced damage.[130] Yao et al used mesoporous silica nanoparticles as carriers to develop a bone-targeted delivery system containing enoxacin (Eno@MSN-D), where aspartic acid (Asp) was used to target the nanoparticles to infected bone sites, enabling phagocytosis of the polyethylene glycol (PEG) coated on the nanoparticles by macrophages (MΦ) and subsequent drug release. In vivo experiments revealed significantly lower bacterial loads at infection sites in Eno@MSN-D-treated rats than in the other groups, demonstrating the system's potent antibacterial efficacy.[131]

Recent studies have also explored combinatorial approaches that integrate nanotechnology with bacteriophages to combat drug-resistant bacteria, utilizing phage-mediated targeting for precise drug delivery. Wang et al developed liposome-phage nanoconjugates (Lip@Phage) to enable targeted antibiotic delivery to bacterial infection sites. The system can degrade both the extracellular polymeric substance (EPS) layer of biofilms and the bacterial cell wall, preventing antibiotic resistance mechanisms from impeding drug efficacy. In vivo studies demonstrated that, compared with the control, Lip@Phage, which has a low antibiotic payload, caused a greater than 1,000-fold reduction in the number of MRSA CFUs at infection sites after two weeks of treatment, resulting in significant bacterial eradication.[37]

Nanotechnology Combined with Immunotherapies

With the updating of antimicrobial concepts for implant-associated infections and the continuous advancement of nanotechnology research, some emerging studies have integrated nanotechnology with immunotherapy for PJI treatment and attempted to develop biomaterials that regulate host immune functions, thereby providing a new direction for localized therapy against antibiotic-resistant bacterial infections.[102] Nanocarriers are typically employed to deliver nucleic acid fragments precisely to local infection sites for immune cell uptake. These nanocarrier-delivered nucleic acids modulate immune pathways, enhancing host-specific immunity to counteract both the biofilm-induced immunosuppressive microenvironment and additional immune evasion mechanisms of drug-resistant bacteria, ultimately achieving effective eradication of localized infections.[82,132–134] Li et al engineered a nanomaterial-based gene delivery system to create an implantable nanoparticle coating capable of the localized generation of chimeric antigen receptor macrophages (CAR-MΦs). The pDNA-laden peptide nanoparticle (pPNP) coating fabricated on titanium implants enables localized pDNA delivery at the bone-implant interface. The delivered pDNA contains both SasA-CAR mRNA and caspase-11 short hairpin RNA (CASP11 shRNA), which induce the entry of surrounding MΦs into CAR-MΦs. The engineered CAR-MΦs then selectively targeted and eradicated MRSA at infection sites (Figure 9). Compared with the control group, the Ti-pPNP group presented a significantly reduced MRSA burden and diminished inflammatory cell infiltration at infection sites, demonstrating effective resistance against drug-resistant bacterial infections. Additional experimental data confirmed the favorable biocompatibility of pPNP coatings.[133] Tang et al's research on combating drug-resistant pathogens in sepsis employed analogous mechanisms, offering inspiration for nanotechnology-integrated combination therapies in PJI. They engineered CRV peptide-modified lipid nanoparticles (CRV/LNP-RNAs) encapsulating both siCASP11 and SasA-CAR mRNAs. CRV-mediated targeting delivered these nucleic acid-loaded lipid nanoparticles (LNPs) into macrophages, inducing CAR-MΦ generation, which subsequently eradicated MRSA. Following a defined treatment period, the CRV/LNP-RNA treatment group presented significantly improved survival rates in MRSA-induced septic mice compared with the other control groups throughout the observation period.[134]

Nanotechnology Combined with Electrical Effects

Transmembrane charge transfer inhibits bacterial growth and biofilm formation by promoting ROS generation, surface electron depletion, respiratory chain disruption, and alterations in cell membrane function.[135–137] This mechanism offers

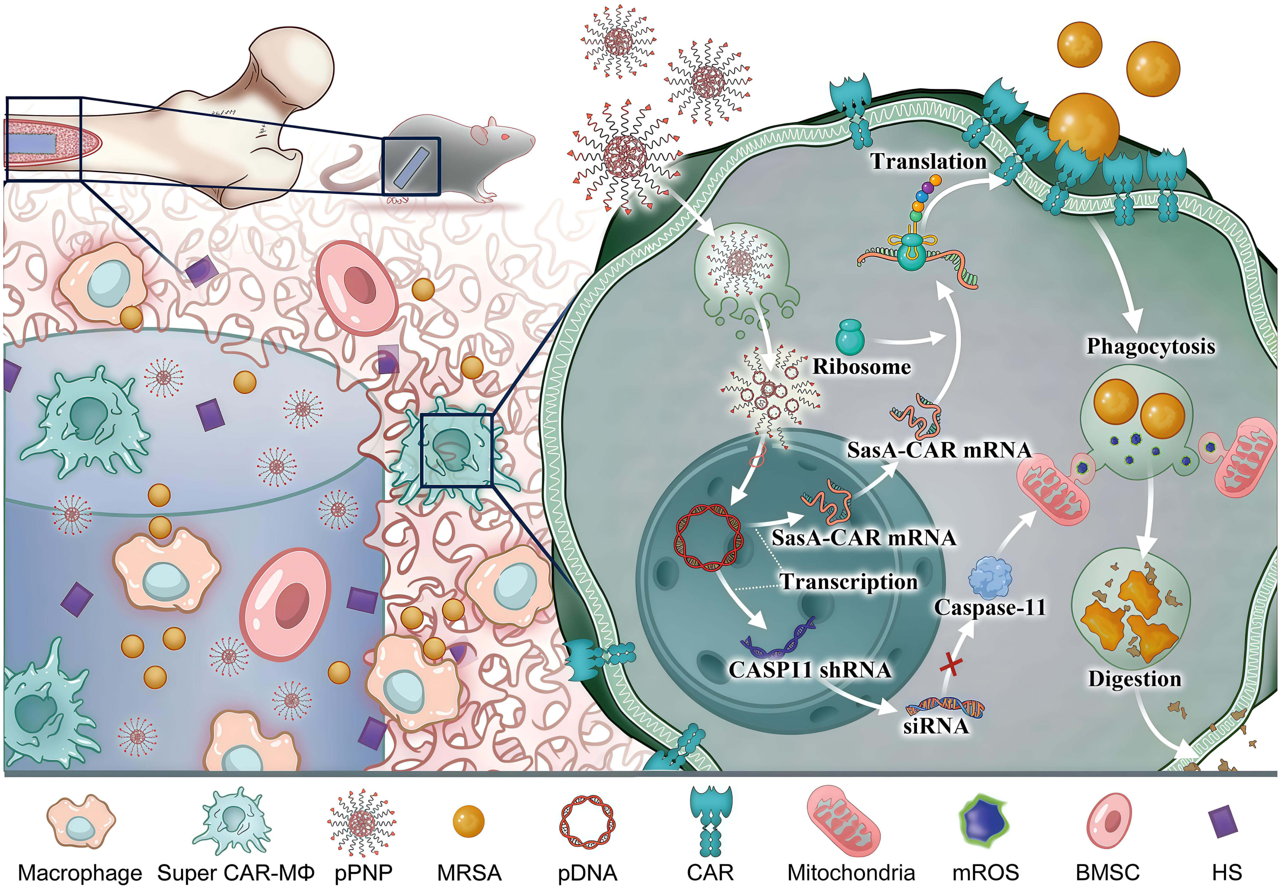

Figure 9 The mechanism of pPNP-induced CAR-MΦ generation and subsequent MRSA eradication. Reproduced with permission.[133] Graphical abstract: Created in BioRender. Li, (Y) (2025) https://BioRender.com/rww55i7.

a novel strategy for antimicrobial nanotechnology. Recent studies have developed electroactive nanoplatforms to trigger bacterial transmembrane charge transfer, achieving physical sterilization.[136,138,139] Wei et al constructed a Bi2S3/FeS2 heterojunction (BFS) with a redox potential lower than the surface potential of Staphylococcus aureus. This potential difference initiates transmembrane electron outflow from bacteria to BFS, sequentially causing respiratory chain disruption, subsequent redox metabolism collapse, and ultimately bacterial death.[140] Fan et al further demonstrated that the electromechanical properties of specific heterojunction structures can effectively induce osteogenic differentiation in bone marrow-derived mesenchymal stem cells (BMSCs).[141] Sieben et al developed an engineered nanohydroxyapatite/MoOx composite coating for orthopedic implants that utilizes extracellular electron transfer (EET) to mediate antibacterial activity. Ultrastructural changes revealed nano-HA/MoOx-induced damage to both Staphylococcus aureus and Pseudomonas aeruginosa, characterized by cell wall/membrane rupture and cytoplasmic leakage. In addition, the antibacterial mechanism showed no cytotoxic effects on rat primary osteoblasts (rOBs), demonstrating excellent biocompatibility.[142] Consequently, the integration of nanotechnology with electroactive effects has significant potential for antimicrobial applications in PJI.

Novel Stimuli-Responsive Nanomaterials

Stimuli-responsive nanomaterials have garnered significant research interest for their tunable antimicrobial capabilities, yet their development has been accompanied by emerging challenges that require resolution.[143] Recent advances in stimuli-responsive nanomaterials have successfully addressed a subset of these challenges, enhancing material tunability while enabling precise targeting of pathogenic bacteria. For example, to address the issue of stimulus-induced nanomaterial hyperthermia or excessive ROS generation, which can damage normal cells, researchers have recently developed multiple mitigation strategies. Li et al developed a zero-dimensional carbon-based nanomaterial (Arg-CD) that is released from composite hydrogels in the acidic environment of infected tissues. The released Arg-CD selectively induces excessive ROS production in bacteria to eliminate them while upregulating antioxidant enzymes in normal cells to prevent ROS-induced oxidative damage.[144] Several research groups have attempted to solve this problem through precise intracellular sterilization. Yang et al developed a nanocomposite named Cu(II)NS-SPA. The nanocomposite, after being taken up by MRSA-infected MΦs, responds to both the endogenous biofilm niche and exogenous ultrasound stimulation to release ROS, achieving precise intracellular MRSA eradication.[145] Mei et al utilized mild photothermal stimulation to increase metabolic activity in Staphylococcus aureus, promoting bacterial uptake of Cu-POM. Once internalized, Cu-POM inhibits the bacterial TCA cycle, achieving precise sterilization through a unique mechanism independent of ROS or thermal effects.[146] To address the antioxidant defense barrier of bacterial biofilms against ROS, Ge et al developed piezoelectric-enhanced metal-organic framework nanocatalysts that generate ROS under photoacoustic stimulation while disrupting the biofilm's antioxidant system through H2S suppression. Moreover, the resulting localized redox imbalance induces N1 neutrophil polarization, which enhances biofilm clearance.[147]

Conclusion

In recent years, increasing bacterial resistance has gradually rendered antibiotics ineffective, making PJI prevention and treatment more challenging. The development of alternative PJI therapies has emerged as a major research focus, which can effectively combat drug-resistant bacteria through either controlled high-concentration antibiotic release or physicochemical mechanisms while maintaining cytotoxicity within safe limits. Consequently, nanotechnology, particularly stimuli-responsive nanomaterials and nanotechnology-based immunotherapy, exhibits significant potential for both treating and preventing PJI, offering substantial clinical advantages and promising future applications.

However, clinical translation remains predominantly confined to the preclinical stage due to safety concerns (cytotoxicity, carcinogenicity, hemolysis, and hepatorenal toxicity) and practical challenges (cost, production efficiency, and in vivo stability). Future studies should address the following aspects: (1) comprehensive safety and toxicological evaluation of nanomaterials prior to clinical translation, along with well-designed trials addressing cost, production efficiency and stability in vivo;[56] (2) comparative assessment of antimicrobial efficacy against diverse PJI pathogens; (3) further development in externally modulated stimulus-responsive nanomaterials for localized drug delivery, novel nanoantibacterial agents, and targeted antibacterial and immunomodulatory nanotherapies;[148–151] (4) development and clinical application of novel nanocarriers; (5) combination strategies integrating nanotechnology with other novel therapeutic approaches. In conclusion, nanotechnology still has

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substantial development potential in PJI prevention and treatment, but more attention and investment are needed to overcome the various challenges associated with its development.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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