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Review Paper

Biofilm-associated Orthopaedic Implant Infections and Periprosthetic Bone Loss: A Mini Narrative Review

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ABSTRACT

Orthopaedic implant-associated infections, including periprosthetic joint infection (PJI) and fracture-related infection, remain formidable challenges due to the resilient nature of microbial biofilms. Biofilms facilitate bacterial persistence by providing phenotypic tolerance to antibiotics and shielding pathogens from host immune clearance, often leading to diagnostic ambiguities and high recurrence rates. This mini-review synthesizes current evidence on biofilm biology and management, contrasting established surgical strategies (debridement, antibiotics, and implant retention vs revision) and local antimicrobial delivery with emerging adjunctive therapies, such as bacteriophages, antimicrobial peptides, and photodynamic therapy (PDT). Furthermore, it delineates the molecular divergence between infection-associated periprosthetic bone loss and aseptic wear-particle osteolysis, highlighting the roles of receptor activator of nuclear factor-κB ligand/receptor activator of nuclear factor-κB/osteoprotegerin, nuclear factor kappa B, and mitogen-activated protein kinase signaling. While preclinical innovations show promise, the transition to clinical practice requires standardized diagnostic frameworks and robust prospective trials.

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Introduction

Orthopaedic implant-associated infection remains one of the most consequential complications in contemporary musculoskeletal surgery. Although the overall incidence of periprosthetic joint infection (PJI) after arthroplasty is relatively low, its burden is disproportionately high because it is associated with repeated surgery, prolonged disability, higher mortality, and substantial economic cost [1-3]. The biological basis of this difficulty lies largely in biofilm formation on implant surfaces. Once microorganisms adhere to foreign materials and establish a mature biofilm, they become markedly less susceptible to both host immune clearance and antimicrobial therapy, which helps explain the chronicity and recurrence that characterize many implant-related infections [4, 5]. Infection is not only a microbiological event but also a potent driver of inflammatory bone loss. Infected implants may therefore fail through a combined process of bacterial persistence, inflammatory tissue injury, and progressive disruption of the bone-implant interface. This overlap is clinically important because infection-associated osteolysis can resemble aseptic loosening, while requiring an entirely different diagnostic and therapeutic approach [5-7].

The pathogenic success of biofilms depends on their structural and ecological complexities. Rather than existing as free-floating organisms, bacteria within orthopaedic infections often organize into a three-dimensional matrix-enclosed community with marked spatial heterogeneity in nutrient access, oxygen tension, metabolic activity, and antimicrobial exposure [8]. This architecture allows different bacterial subpopulations to survive under conditions that would normally be lethal to planktonic organisms. In addition, polymicrobial behavior can further increase treatment difficulty. Interactions among species may be cooperative, neutral, or competitive, but in several experimental settings they have been shown to enhance microbial persistence and alter susceptibility to therapy [9-12]. Some organisms can physically or metabolically protect neighboring bacteria, whereas antibiotic stress itself may paradoxically stimulate biofilm formation in certain contexts [9-12]. These observations underscore an important principle: Implant infection cannot be understood simply as a matter of microbial presence, because the organization of the microbial community strongly influences treatment response.

This biology has substantial diagnostic and therapeutic implications. In PJI and related implant infections, conventional cultures may fail to identify organisms when bacteria are embedded within biofilms or exposed to prior antibiotics. Accordingly, contemporary diagnostic strategies increasingly emphasize structured criteria and multimodal testing. The EBJIS framework, for example, recognizes a graded spectrum ranging from infection unlikely to confirmed infection, helping clinicians interpret imperfect data in a more clinically meaningful way [1]. Adjunctive techniques, such as sonication, optimized tissue sampling, and molecular approaches, including metagenomic and sequencing-based diagnostics, may improve pathogen detection, particularly in chronic or culture-challenging cases [6, 7]. Even so, no single diagnostic tool fully resolves the difficulty of distinguishing indolent infections from presumed aseptic loosening, especially when inflammatory and radiographic findings overlap [6, 7].

Despite advances in adjunctive technologies, the importance of surgical management remains unchanged. Source control continues to be the foundation of treatment, because mature biofilm cannot reliably be eradicated by antibiotics alone [13, 14]. In carefully selected acute cases, debridement, antibiotics, and implant retention may provide infection control when the implant is stable, and the duration of symptoms is limited [13, 14]. In contrast, chronic infection, extensive biofilm maturation, loosening, sinus formation, or substantial bone loss often necessitate implant exchange, either as a one-stage or two-stage strategy depending on host factors, soft-tissue status, microbiology, and local reconstructive considerations [13, 14]. In this respect, new technologies should be understood as supportive rather than substitutive; they may improve eradication or reduce recurrence, but they do not remove the need for appropriate surgery.

Therefore, interest in biofilm-directed therapies has expanded considerably. Antimicrobial photodynamic therapy (PDT) is one such approach. By activating a photosensitizer, such as 5-aminolevulinic acid, PDT generates reactive oxygen species capable of damaging microbial cells within the biofilm matrix [8]. Because this mechanism does not depend on conventional antibiotic targets, it may retain activity even when classical resistance mechanisms are present. Experimental models, including microfluidic systems, have reported marked reductions in biofilm burden and superiority over commonly used local antimicrobial or antiseptic solutions in some settings [8]. However, these findings should be interpreted with caution. Most evidence remains preclinical, and important clinical questions remain unresolved, including optimal dosing, penetration in deep tissue environments, repeat treatment schedules, and integration into real surgical workflows [8].

Bacteriophage therapy is a different but equally promising strategy. Phages are viruses that infect bacteria with high specificity, and their theoretical advantages include bactericidal activity, the ability to spare eukaryotic cells, limited disruption of normal flora, and absence of conventional cross-resistance with antibiotics [8]. They may be particularly useful in biofilm-associated infections because some phages produce depolymerases, lysins, or proteases that help degrade extracellular matrix and improve access to embedded bacteria [8, 10-12]. In addition, phages do not depend on tissue concentrations in the same way as standard antibiotics, since successful activity is mediated by receptor recognition and bacterial infection rather than only passive diffusion [8, 10-12]. Nevertheless, enthusiasm should be tempered by practical limitations: phage resistance may emerge, host-pathogen-phage matching is complex, and the existing human data remain limited, often relying on compassionate-use cases rather than controlled trials [8, 10-12].

The challenge of infection prevention is especially evident in open fractures, where contamination, soft-tissue compromise, vascular disruption, and the frequent need for fixation or grafting create ideal conditions for bacterial adherence and biofilm formation [15, 16]. In such injuries, early systemic antibiotics remain a cornerstone of prevention, and administration within the first hour has been associated with lower infection risk [17]. However, tissue delivery is not uniform across injury severities; for example, cefazolin may achieve acceptable levels in Gustilo type II and IIIA injuries while performing less reliably in more devascularized IIIB wounds [18]. Irrigation strategy is another area of continued evolution. Although saline remains widely accepted, iodine-based and biofilm-disrupting solutions are being investigated for their ability to reduce contamination without causing unacceptable tissue toxicity [19, 20]. Likewise, local antimicrobial prophylaxis has gained traction. Vancomycin powder appears to reduce gram-positive infection burden in some settings, and broader local coverage may be achievable when combined with tobramycin, though evidence is not uniform across all fracture types [21, 22]. The presence of implants and graft materials further amplifies risk because any foreign surface can serve as a scaffold for bacterial attachment and early biofilm development [23-25]. As a result, strategies, such as antimicrobial coatings and locally eluting biomaterials, have become attractive tools for prevention during the vulnerable early postoperative window [25].

Local antibiotic delivery is also relevant once infection is established. In poorly perfused tissues, systemic therapy alone may not produce the concentrations required to suppress biofilm-protected organisms. Local delivery systems can achieve high antibiotic levels at the target site while avoiding toxicities associated with prolonged systemic exposure [22, 26-35]. Vancomycin and tobramycin are the agents most commonly used in local form. Clinical studies, such as the VANCO trial, have shown reduced gram-positive infections and modest absolute reductions in deep infection risk in selected lower-extremity fracture populations [26]. Combination local therapy may further improve coverage, though benefits appear context-specific and not universal [22, 27]. Calcium-sulfate carriers have also been used as antibiotic-eluting adjuncts and have shown encouraging infection-control results in some series [31-33]. However, local therapy is not complication-free. Hypercalcemia, persistent wound drainage, and nephrotoxicity under high cumulative aminoglycoside exposure remain relevant concerns [22, 26-35]. Importantly, evidence from OVIVA established that oral therapy can be noninferior to intravenous therapy for many complex bone and joint infections, reinforcing that the route of antimicrobial delivery should be individualized and that local treatment is an adjunct, not a replacement for a well-designed systemic regimen [36].

A broader understanding of orthopaedic infection also requires situating implant infection within the spectrum of musculoskeletal infectious disease. Osteomyelitis, soft-tissue infection, septic arthritis, tenosynovitis, bursitis, myositis, fracture-fixation infection, and PJI differ in tissue biology, microbiology, and treatment requirements, yet many of them share the same core problem when foreign material is present: Avascular surfaces and necrotic tissue create protected niches in which antibiotics and host immune cells function poorly [37-39]. This is particularly relevant in chronic osteomyelitis, where sequestrum and impaired perfusion sustain infection despite treatment [37, 40-44]. Similarly, fracture-fixation infection and chronic PJI illustrate how biofilm convert an initially acute infectious process into a persistent interface disease, often accompanied by loosening and structural compromise [38, 39, 45]. The practical consequence is that implant retention becomes progressively less viable as biofilm matures and mechanical failure develops.

Distinguishing between infection-associated bone loss and aseptic periprosthetic osteolysis is one of the most important conceptual points in this field. Aseptic osteolysis has classically been linked to wear debris generated from polyethylene, metal, ceramic, or cement, which is then phagocytosed by macrophages and other cells of the innate immune system [46-51]. This initiates a cascade involving tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, chemokines, inflammasome activation, altered macrophage polarization, and stimulation of osteoclastogenesis [51-54]. Several of these responses converge on the receptor activator of nuclear factor-κ\ kappaκB ligand (RANKL)/RANK/osteoprotegerin (OPG) axis and downstream transcriptional programs that promote osteoclast differentiation and bone resorption. Mechanical unloading may further aggravate these processes through osteocyte-derived signaling, including increased RANKL and sclerostin expression [55-58].

Among these molecular systems, the RANKL/RANK/OPG pathway plays a central role in osteoclast regulation. RANKL, produced by osteoblast-lineage cells, activated T cells, endothelial cells, and particularly osteocytes, binds RANK on osteoclast precursors and drives osteoclastogenesis via TRAF6, nuclear factor kappa B (NF-κB), mitogen-activated protein kinase (MAPK), and NFATc1 signaling. OPG acts as a decoy receptor that limits this interaction, and imbalance between RANKL and OPG favors bone resorption [59-63]. In periprosthetic osteolysis, inflammatory cytokines can increase RANKL and suppress OPG, thereby amplifying osteoclast activity [59-64]. These observations make antiresorptive strategies conceptually attractive, including the possible use of agents, such as denosumab, although systemic adverse effects, impaired bone remodeling, and delivery challenges remain unresolved [65, 66].

NF-κB is another major hub linking inflammatory signaling to osteoclast activation. Wear particles and inflammatory ligands can stimulate canonical NF-κB activation through pattern-recognition pathways, increasing expression of TNF-α, IL-1β, IL-6, monocyte chemoattractant protein-1, and osteoclast-related genes [60, 64]. This not only amplifies local inflammation but also enhances precursor sensitivity to RANKL and promotes bone destruction. Multiple experimental interventions have attempted to inhibit NF-κB signaling by targeting IκB kinase complexes, upstream kinase regulation, proteasomal degradation, or RNA-based silencing. However, this pathway is deeply embedded in host defense and cell survival, indicating that broad inhibition can impair bacterial clearance or produce off-target toxicity. As a result, therapeutic translation will likely require highly selective and preferably local modulation rather than systemic pathway suppression [60].

MAPK/extracellular signal-regulated kinase (ERK) signaling contributes another layer of complexity. ERK, p38, and c-Jun N-terminal kinase regulate osteoclast precursor survival, differentiation, maturation, fusion, and resorptive function, with substantial redundancy and crosstalk among branches [61]. Therefore, blocking one arm of the pathway may not produce durable benefits if alternative branches compensate [61]. Preclinical studies have explored pharmacologic inhibitors, natural compounds, and gene-silencing approaches to reduce osteolysis through MAPK modulation [61]. Bisphosphonates may also affect osteoclast biology through the mevalonate pathway and downstream signaling effects, though interpretation of their clinical benefit in periprosthetic bone preservation requires caution and endpoint-specific analysis. These data are promising mechanistically, but they remain far from establishing a standardized host-directed therapy for infection-associated bone loss [65, 66].

Newer antibiofilm and host-modulating technologies seek to bridge this gap. Antimicrobial peptides, depolymerases, endolysins, quorum-sensing inhibitors, nanoparticles, hydrogels, extracellular vesicles, and small interfering RNA platforms aim to disrupt biofilm integrity, deliver payloads more efficiently, or attenuate osteolytic signaling [67-69]. An ideal future system may need to perform both functions simultaneously: reducing microbial burden while limiting inflammatory bone destruction. This dual-purpose concept is attractive, particularly for chronic implant infections in which biofilm persistence and interface osteolysis reinforce one another [67-69]. However, current evidence is still dominated by laboratory and animal models, many of which do not capture the full reality of human chronic infection, including polymicrobial biofilms, repeated antibiotic exposure, necrotic tissue, dead space, implant instability, and mechanical loading [67-69]. Surrogate improvements in colony counts, biomass, or cytokine expression alone cannot establish clinical value [67-69].

This translational gap is a major limitation of this field. The most relevant outcomes are not simply bacterial reduction in vitro, but durable infection eradication, implant survival, preservation of bone stock, reduction in reoperation, acceptable complication profiles, and meaningful gains in pain and function [67-69]. Therefore, any emerging therapy must be judged against the current standards of meticulous diagnosis, appropriate surgery, and well-targeted antimicrobial therapy, rather than against laboratory endpoints alone [65, 66]. The same

caution applies to host-directed molecular interventions: reducing osteoclast activity may appear beneficial, but excessive immune suppression could be counterproductive in an infected environment [60].

Conclusion

In conclusion, orthopaedic implant infection is sustained by the interaction of biofilm architecture, impaired antimicrobial penetration, immune evasion, persistent inflammation, and mechanical compromise at the implant-bone interface. These processes contribute not only to microbial persistence but also to progressive bone loss that may mimic or coexist with aseptic periprosthetic osteolysis. Contemporary care still depends on accurate diagnosis, timely surgical source control, and individualized antimicrobial treatment. Although bacteriophages, PDT, antimicrobial coatings, local delivery systems, nanoparticles, and molecular pathway modulation are promising, most remain adjunctive and investigational rather than definitive standards of care. Future progress will depend on therapies that can both control biofilm and preserve periprosthetic bone while demonstrating real, durable, patient-centered benefits in clinical practice.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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