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Current Options and Emerging Biomaterials for Periprosthetic Joint Infection

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Abstract

Purpose of Review—Infection in the setting of total joint arthroplasty, referred to as periprosthetic joint infection (PJI), is a devastating complication requiring prolonged and costly treatment. The unique environment around an artificial joint and ability of surrounding tissues to sequester bacteria collectively make prevention, diagnosis, and treatment of this condition challenging. In light of the unique pathogenesis of PJI, this review explores the limitations of contemporary treatments and discusses novel treatment options.

Recent Findings—Recent advancements in local antibiotic delivery platforms for preventing and treating PJI include titanium nanotube arrays, synthetic polymers, resorbable hydrogels, and cyclodextrin-based drug delivery options. In particular, cyclodextrins have facilitated great advancements in other clinical disorders and have demonstrated early promise as a future option in the arena of PJI.

Summary—Novel treatment modalities for PJI optimize the implant surfaces to prevent bacterial biofilm formation or provide prolonged intra-articular antibiotic dosing to eradicate bacteria.

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Keywords

Periprosthetic joint infection; Controlled antibiotic release; Polymethylmethacrylate; PMMA; Calcium sulfate; Cyclodextrin

Introduction

Periprosthetic joint infection (PJI) following total joint arthroplasty (TJA) is a devastating complication that requires complex and costly treatment. Achieving a clinical diagnosis of PJI can be challenging and upon identifying the causative organism, treatment often involves prolonged systemic antibiotic therapy and multiple revision surgeries. Despite such rigorous treatment measures, PJI patients report significantly poorer quality of life measures [1] and face significantly higher 5-year mortality rates [2] compared to non-infected TJA patients. One of the main reasons PJI occurs and is consequently difficult to eradicate is the ability of bacterial biofilms to resist mechanical debridement and antibiotics. The purposes of this review are to detail the increasing clinical and financial burden of PJI, to describe the unique pathophysiology found within an infected joint replacement, and to contrast the limitations of contemporary treatment methods with promising novel treatment modalities which are being developed.

Quantifying the Burden of Periprosthetic Joint Infection

The incidence of PJI is reported to be 0.75–1.24% for primary total hip arthroplasty (THA) and 0.3–1.28% for primary total knee arthroplasty (TKA) [3,4]. The incidence is unfortunately higher for revision THA (1.6 to 3.96% at 1–2 years; [5,6]) and revision TKA (0.9% in the first 30 days and 4.6% at 2 years [7,8]). Furthermore, PJI is the most common reason for revision TKA and is the second most common reason for revision THA, accounting for 24–30% of TKA revision and 11–30% of THA revisions [5,9–11]. The morbidity of undergoing revision surgery for PJI should not be underestimated. When compared to non-infection revisions, PJI patients have a 3.25-fold higher chance of mortality within the first 30 days after surgery [8], with their overall mortality rate approaching 8–10 and 26% at 5 years [12,13].

The economic burden of PJI is rising and is projected to exceed \$1.62 billion in the USA alone by the year 2020 [14]. The average cost to the healthcare system for a single patient requiring treatment and revision surgery for PJI is \$96,166, a figure that is five times higher than the cost of a primary joint replacement [15]. Currently, PJI consumes over 50% of inpatient resources allocated for revision knee surgery and will reach a similar level of consumption for revision hip surgery resources by 2025 [14]. Due to the costs required to manage PJI, guidelines have been published by academic authorities from both orthopedic surgery and infectious disease societies in an attempt to standardize the prevention and treatment of PJI [16–18]. Despite such initiatives, the number of PJI cases are still expected to rise over the next decade, prompting PJI researchers to reconsider the pathophysiology of implant infection.

The Pathophysiology of PJI: the Periprosthetic Environment and “Race for the Surface”

The insertion of an artificial joint replacement effectively separates two markedly different environments: (1) the articular space, which is poorly vascularized, filled with synovial fluid and tolerant to bacterial antigen exposure [19] and (2) the intramedullary space, which is well vascularized, hypercellular, and generally sensitive to bacterial exposure. In clinical PJI, bacterial infiltration is most often identified in the articular space and is commonly believed to occur either due to perioperative contamination or, in the chronic setting, due to hematogenous spread [20]. The articular space is relatively immune-privileged, suggesting that bacteria could proliferate substantially before stimulating a local immune response. A delayed or impaired local immune response within the articular space could explain why PJI secondary to fungal infections or slow-growing bacteria (such as *P. acnes*) present with intermittent symptoms and normal serological inflammatory markers [21].

The Implant Surface

Periprosthetic joint infection involves bacterial colonization of the implant surface. Following surgical implantation of the joint replacement, contaminating bacteria as well as fibro-blasts, macrophages, and host proteins are available to occupy the implant surface [22]. Competition for space on the implant surface is commonly referred to as a “race to the surface.” If the host cells and proteins are established first, colonization by bacteria is less likely.

Artificial joint replacements consist of combinations of cobalt-chrome, titanium, ceramic, and polyethylene (plastic) implants. Although bacteria are capable of proliferating on each of these materials [23], several surface properties can influence the adhesion process. Roughened surfaces, generally found on metal implants (alloys of cobalt-chrome or titanium), have been shown to enhance bacterial colonization if the surface roughness profile approaches the size of an individual bacteria (1 μm), and to inhibit colonization if surface pores are similar in size to osteoblasts [24]. Factors like high surface hydrophobicity and low surface free energy, as found on cobalt-chrome surfaces, have been shown to inhibit bacterial surface proliferation [23]. Finally, implant surface porosity can influence fluid flow at the implant surface, thereby impairing or enhancing bacterial adhesion [25].

Bacteria and Biofilm

The two microorganisms most commonly responsible for clinical PJI are *Staphylococcus aureus* (*S. aureus*) and coagulase-negative staphylococcal species (*Staphylococcus epidermidis*) [26]. Both bacterial species are commonly found on human skin. Once inside the articular space, these organisms use lipopolysaccharide processes and proteinaceous adhesins to adhere to an implant surface [19]. Upon adherence, bacterial RNA transcription changes dramatically, shifting to anaerobic processes and secretion of a polysaccharide matrix which is deposited on the implant surface and around the bacteria to form the biofilm [27]. The physical barrier provided by the extra-cellular matrix and the changes in physiology of resident bacteria permit the biofilm colony to resist many commonly used

antibiotics (including vancomycin, rifampicin, tigecycline, ciprofloxacin, clindamycin, cloxacillin, daptomycin, trimethoprim/sulfamethoxazole, fosfomycin) [26].

Antimicrobial Resistance

To help prevent PJI, antibiotics are often added to bone cement. Two commonly used antibiotics within bone cement are gentamycin and tobramycin, selected due to their broad spectrum and ability to withstand increases in local temperature caused curing of the bone cement [28]. Although standard antibiotics applied in these cases are effective against *S. aureus* and *S. epidermidis*, resistant strains of these organisms are increasingly prevalent. Anguita-Alonso and colleagues examined the resistance profiles of 93 different staphylococci isolates from PJI patients and found that up to 41% of the staphylococci cultures were resistant to gentamicin and 66% of isolates were resistant to tobramycin [28]. The brief and erratic nature by which bone cement elutes antibiotics into the articular space further impairs their antimicrobial effectiveness [28]. Furthermore, in addition to resistance against antibiotics within bone cement, recent serological studies of patients undergoing TJA have shown that when intravenous vancomycin is given before surgery to prophylactically prevent PJI, the dose given is either insufficient to achieve proper bacteriostatic concentrations [29], or is high enough to cause acute kidney injury [30]. Therefore, significant efforts are needed both to improve the use of antibiotics within bone cement and systemically to prevent the onset of PJI.

Colonization of Bone

In addition to the articular space, the microscopic bony architecture that is adjacent to an artificial joint also provides a unique environment for bacterial colonization. Recent investigations have demonstrated that nanoscale pores within osteocyte lacunae can serve as areas of bacterial infiltration. de Mesy Bentley and colleagues observed individual *S. aureus* bacteria extend themselves into sub-micron spaces within the osteocytic lacunar-canalicular network of bone tissue [31]. They found that bacteria sequestered within these osteocyte lacunae were protected from macrophages by the mineralized matrix, thereby protecting the colony of *S. aureus* from the immune system. The ability of *S. aureus* to traverse canaliculi is unexpected because osteocyte canaliculi are one third the size of the *S. aureus* microbe (canaliculi are ~ 300 nm in diameter, while *S. aureus* are typically 1000 nm in diameter). Although the characteristics of bacteria that influence penetration into nanoscale pores such as cell stiffness and deformability are not yet known, bacteria present within osteocyte lacunae not only are protected from macrophages but also are located further from the systemic circulation, potentially reducing exposure to systemically administered antibiotics.

Contemporary Treatment of PJI: Limited Success

The current “gold standard” treatment for chronic PJI is the “two-stage revision.” This treatment begins with a “first stage” surgery, where the infected artificial joint replacement is removed, the infected tissues are debrided, and a temporary bone cement spacer containing high concentrations of antibiotics is inserted, and postoperative organism-specific intravenous antibiotic therapy [24,32,33]. Antibiotics are continued for 6–12 weeks until inflammatory markers normalize. Subsequently, a “second stage” is performed whereby the

cement spacer is removed, and a new artificial joint replacement is inserted. Overall, the two-stage revision process takes several months to complete and profoundly impacts patients and their families [34]. Yet despite undergoing such invasive treatment, two-stage revisions have failure rates of up to 22% [7, 35–37]. An alternative treatment strategy to reduce patient morbidity includes trying to condense treatment into a single surgical procedure (a “single-stage revision”), but this approach only routinely succeeds in patients with minimal comorbidities and non-resistant bacterial infections [38]. Another advocated treatment after failed revision surgery is to suppress PJI through lifelong antibiotic therapy. Although less morbid, side effects from prolonged antibiotic use and emergence of resistant organisms make lifelong suppression a less appealing choice [39].

Therefore, there is interest from both clinicians and fundamental researchers in optimizing contemporary PJI treatments and developing novel adjuncts which can more effectively reduce bacterial and biofilm burden and lead to a higher chance for treatment success. Furthermore, given that the number of revision arthroplasty surgeries are expected to rise to 65,000 per year in the USA alone [40], there is increasing interest from both the implant industry and state-supported research funding agencies to support PJI treatment innovations.

Optimizing Current Treatments: Beyond Bone Cement

Adding antibiotic powder to bone cement (polymethylmethacrylate or PMMA) was first described over 50 years ago as a method of PJI prevention and is currently routinely performed in primary cemented joint replacements in most countries [37]. Despite the inherent logic of placing an antibiotic depot (often 0.5 g per 40 g of PMMA) within the articular space, the actual preventive effect of antibiotic-loaded PMMA has not been conclusively demonstrated in the orthopedic literature [41]. Furthermore, when higher quantities of antibiotics (2–4 g per 40 g of PMMA [42]) are placed within the articular space in the form of a bone cement spacer to treat PJI, retrieval studies have demonstrated that offending bacteria remain alive within the surrounding tissues [43]. More recent investigations have revealed the limitations of using PMMA as a method of antibiotic-delivery: antibiotics rapidly elute within the first 24 h, but logarithmically decline over a matter of days [44]; antibiotic release is limited to the outer 100 µm layer of the PMMA [45]; and that prolonged sub-therapeutic intra-articular concentrations of antibiotic can undesirably lead to the development of drug-resistant bacteria [24].

In response to the above limitations, investigators have responded by changing the mixing process of PMMA to increase porosity and improve elution profiles [44], using binding agents to increase elution [46] and using newer antibiotics with longer half-lives in an effort to prolong their intraarticular effects [47]. More recently, good PJI treatment success rates have been reported by introducing a percutaneous catheter at the time of revision surgery and regularly infusing antibiotics into the joint space for several weeks [48]. Although such enhancements to contemporary techniques are currently relegated to retrospective case reviews, randomized trials comparing treatment methods are ongoing [49] and will hopefully reduce heterogeneity in the manner by which PJI is currently treated [50]. Moving forward, alternative biomaterials that could eventually replace PMMA represent the next exciting target in PJI research. Yet in order for such a material to succeed clinically, it must

be able to mechanically support physiological loading and simultaneously resist or even remove bacterial colonization.

Novel Treatment Modalities

Commercially Available Alternative Biomaterials

A variety of commercially available biodegradable bone graft substitutes are attractive alternatives to PMMA for filling bone voids. Calcium sulfate, the most commonly used resorbable bone graft substitute, can be molded intra-operatively into radiopaque beads that resorb in 30–60 days. The resorbable nature of this material allows implantation without a second surgery for removal. In vitro studies of antibiotic-loaded calcium sulfate have demonstrated equivalent or better elution characteristics when compared to PMMA [51,52]. Preparation of calcium sulfate does not cause the high polymerization temperatures seen with PMMA; therefore, it carries a theoretical advantage of using a wider range of antibiotics. Howlin et al. reported that calcium sulfate beads impregnated with tobramycin and/or vancomycin demonstrated the ability to decrease *S. aureus* biofilm formation over several days, but were not able to eliminate pre-existing biofilms [53]. Unfortunately, clinical studies using calcium sulfate beads have identified several cases of persistent serous wound drainage and heterotopic ossification secondary to possible hyper-sensitivity reactions. [54•,55]. With regard to treating orthopedic infections, clinical studies have demonstrated treatment benefits with antibiotic-loaded calcium sulfate products in the setting of osteomyelitis [54•,56]. One randomized clinical trial of tobramycin delivery via calcium sulfate beads versus PMMA beads in 30 patients with osteomyelitis demonstrated an infection clearance rate of 86% in both groups with significantly fewer revision procedures required in the calcium sulfate group [57]. Clinical data supporting regular use of calcium sulfate for antibiotic delivery in joint replacement surgery is limited. One report of 32 patients with PJI treated with irrigation and debridement, calcium sulfate beads, and implant retention demonstrated an unacceptably poor rate of treatment failure of 48% [58•]. McPherson et al. reported on a heterogeneous cohort of 250 patients undergoing aseptic revision, single-stage revision for PJI, or two-stage revision for PJI [55]. Vancomycin and tobramycin were used in calcium sulfate beads at each surgery and results demonstrated an overall 2.4% failure due to recurrent infection or new infection. Finally, a cohort of 15 patients treated with single-stage revision and calcium sulfate beads reported a 20% rate of hypercalcemia, with one of three patients with hypercalcemia requiring treatment for this complication [59]. Commercially prepared calcium sulfate with tobramycin (OSTEOSET, Wright Medical) has been approved for use in other countries; however, antibiotic-laden calcium sulfate is not yet approved for use in the USA.

Additional biodegradable bone substitute materials have been investigated for the treatment of orthopedic infections, including bioactive glass, and various combined biocomposites [60]. However, the FDA has not approved most agents for antibiotic delivery, since evidence for their clinical efficacy is lacking [54•]. One recent example with limited supporting data is Septacin, a commercially available polyanhydride biodegradable material loaded with gentamicin that can be placed near the surgical site to prevent infections [61,62]. The theoretical benefits of antibiotic release from these biodegradable options have yet to be

validated in well-designed clinical studies and may not preclude the necessity for two-stage revision surgery. Moving forward, a lingering limitation of existing resorbable bone substitutes is that the rate of resorption is typically faster than the ingrowth of surrounding bone. Hence, resorbable bone substitutes only provide mechanical support for a relatively short time period and therefore are not appealing solutions for revision joint replacement constructs which are expected to last for the long term.

Titanium Nanotube Arrays

Local delivery of antibiotics the use of nanotube arrays processed on the surface of titanium represent another innovative method of preventing PJI. In vitro experiments have demonstrated sustained release of gentamycin for a duration of 11 days from the surface of titanium alloys coated with nano-tube arrays [63]. Similarly, non-antibiotic antimicrobial peptides with broad-spectrum activity have demonstrated sustained release from titanium nanotubes for 7 days. Although this technology is promising for multi-drug delivery options, its effect on osseointegration onto titanium surfaces requires more investigation.

Implant Coatings With Antibacterial Effect

As an alternative to drug-eluting antibacterial coatings and nanotubes, several groups have developed orthopedic coatings that intrinsically repel or kill bacteria. Silver nanoparticles are one of the most common non-antibiotic antibacterial coatings [64–76]. In these settings, silver ions leach from the coating, diffuse into bacterial cells, and damage enzymes in the cell [66]. Specifically, several nanosilver formulations have been developed in which the silver is slowly solubilized over an extended period of time, preventing excessive local concentrations [66]. The nanosilver biopolymer composite films can be formed in a variety of shapes that are active against both *E. coli* and *S. aureus* for 10 days without cytotoxicity towards osteoblasts [68,73]. Additionally, only 7% by weight of the loaded silver was released from their coatings after 28 days, demonstrating the long-term antibacterial activity potential of their coating [73]. Other similar coatings have incorporated silver nanoparticles into hydroxyapatite and chitosan to create an antibacterial coating that promotes osseointegration [71,72]. These coatings have shown over a 90% reduction of both *E. coli* and *S. aureus* surrounding the implant [72]. Furthermore, titanium dioxide and silver nanoparticles have been combined in order to make the antibacterial coatings anticorrosive [64,75]. While these novel materials have been explored in a translational setting, they yet to be clinically evaluated in an orthopedic setting [77].

Polymers

Synthetic polymers such as poly(lactic acid), poly(caprolactone), and poly(lactic-co-glycolic acid) have been studied in in vitro and in animal models to provide sustained release of antibiotics via diffusion and hydrolytic bulk degradation [54••]. The most studied synthetic polymer poly(lactic acid-co-glycolic acid) (PLGA) has shown greater efficacy for antibiotic delivery compared to systemic administration and local delivery with PMMA [54••]. Alternatively, poly(caprolactone)-poly(quaternary ammonium salt) micelles are copolymers that have intrinsic antibacterial effect. When combined with the antibacterial drug triclosan, investigators showed that these micelles also have the ability to function as carriers for drug delivery. The combination of poly(caprolactone)-poly(quaternary ammonium salt) micelles

with triclosan had a synergistic antimicrobial effect when tested against *Escherichia coli* [78]. Finally, polymeric drug-eluting “sleeves” or covers for orthopedic devices have been patented by Boston Scientific Inc. and Control Delivery Systems Inc.; however, they have not been widely implemented in clinical settings [79,80].

Hydrogels

Recent innovations have allowed researchers to coat an implant with a quickly resorbable hydrogel that contains one or multiple antibiotics, thereby delivering the without impeding osseointegration [81]. Drug delivery using alginate-based hydrogel matrices has been compared to that using composite gelatin and hydroxyapatite matrices. In vitro sustained release of ciprofloxacin increased from 5 h in the composite matrix to 10 days in the alginate matrix [82]. Similarly, polysaccharide membranes of sodium alginate and gellan gum crosslinked with calcium ions have demonstrated release of gentamicin over a period of 21 days [83]. These polysaccharide membranes also have the added benefit of intrinsic antimicrobial activity, conferring dual functionality.

Cyclodextrin-Based Drug Delivery

Cyclodextrins are another class of drug delivery approaches with potential for use in orthopedic applications. Cyclodextrin is a cyclic oligosaccharide comprised of 6–8 glucose monomers with a hydrophobic interior and relatively hydrophilic exterior [84]. When cyclodextrin is crosslinked with an insoluble polymer, pharmaceuticals can form an inclusion complex with “pockets” of cyclodextrin to facilitate a controlled and prolonged release of the drug. Drug release from cyclodextrin polymers is based on chemical affinity between the drug and the cyclodextrin pockets. The affinity-based release from cyclodextrin pockets does not follow the burst release pattern seen with the more common diffusion-based release, thereby allowing for slow drug release even from thin coatings [85–87].

In its insoluble form, cyclodextrin has been incorporated into a number of non-orthopedic implants including hernia meshes [88], vascular grafts [89], and stents [90] to deliver antibiotics over an extended period of time [91–98]. Furthermore, recent in vitro efforts have shown that cyclodextrin biomaterials may be refilled with pharmaceuticals even when the material is covered by a biofilm, allowing for additional windows of therapeutic treatment long after implantation (Fig. 1(b)) [99••]. This refilling functionality enables cyclodextrin to be implanted without drug and filled with a selected drug or antibiotic “on demand” via a simple external bolus injection into nearby tissue. Refilling enables clinicians to administer antibiotics selectively to indicated patients (i.e., only if the patient presents with infection), rather than exposing all patients to systemic antibiotics. Preliminary in vivo animal studies have demonstrated the effectiveness of refilling for cyclodextrin-coated hernia meshes [88].

For orthopedic applications, cyclodextrin has been functionalized to hydroxyapatite [93,95,98], incorporated into a chitosan nanoparticle coating [91], and coated on bone screws and Kirschner wires [92]. Specifically, Thi et al. and Lepretre et al. grafted hydroxypropyl- β -cyclodextrin onto microporous hydroxyapatite discs and loaded the discs with ciprofloxacin and vancomycin [93,95]. In this study, antibiotics were released into a simulated in vivo environment to evaluate the drug distribution at the infection site in an

effort to develop more effective treatments for osteomyelitis [95]. Implants functionalized with cyclodextrin showed a sustained antibiotic release over 150–300 h. Lepretre et al. demonstrated that cyclodextrin-functionalized implants had increased bacteriostatic activity against *S. aureus* and improved osteoblast cytocompatibility [93]. Similarly, Taha et al. grafted cyclodextrin onto hydroxyapatite-coated titanium hip implants and loaded both tobramycin and rifampicin in combination [98]. The goal of the dual drug delivery system was to have broad-spectrum coverage against both *S. aureus* and *Enterobacter cloacae*. The system was capable of sustained release of both antibiotics. Furthermore, Taha et al. also have demonstrated antibacterial activity of gentamicin-loaded plasma-sprayed hydroxyapatite-coated titanium functionalized with cyclodextrin [94].

In another orthopedic application, Mattioli-Belmonte et al. developed a chitosan/cyclodextrin nanoparticle coating for titanium [91]. The chitosan nanoparticles were functionalized with sulfobutyl ether- β -cyclodextrin and γ -cyclodextrin and were capable of 20-fold reduction in two *S. aureus* strains in vitro and a sustained release over 7 days. Additionally, the nanoparticle coating demonstrated no significant cytotoxicity towards osteoblasts [91]. Furthermore, Thatiparti et al. directly coated both stainless steel bone screws and Kirschner fracture fixation wires with cyclodextrin crosslinked with 1,6-diisocyanatohexane (HDI) and 2-isocyanatoethyl 2,6-diisocyanatohexanoate (LTI) [92]. The devices were loaded with rifampicin, novobiocin, and vancomycin and demonstrated a sustained release over 200 h. Coated devices were capable of inhibiting the growth of *S. aureus* over 28 days. While promising technology, these coatings have yet to be evaluated in translational in vivo and clinical settings.

Conclusion

PJI is a rare, but devastating complication of total joint arthroplasty that can negatively change patients' lives and attribute significant cost to the health care system. Current clinical treatment for PJI involve morbid surgery, ineffective antibiotic delivery vehicles and can fail up to 22% of the time. Novel treatment modalities for PJI mostly target optimizing the implant surface to prevent bacterial biofilm formation or providing prolonged intra-articular antibiotic dosing to eradicate planktonic bacteria. Cyclodextrin polymers in particular have facilitated great advancements in other disorders and show early promise as an eventual option for clinical use for the treatment of PJI.

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Fig. 1.

(a) Daily release profile from cyclodextrin (CD) (affinity-based) polymers as compared to drug release through diffusion (example: PMMA). Diffusion-based release results in a large bolus of drug release in the first few days (potentially cytotoxic) and sub-inhibitory release at later times. In contrast, release from cyclodextrin polymers is affinity-based, extending release within the desired treatment window for longer periods of time and avoiding an initial bolus effect. (b) Polymers that use affinity-based release may be refilled after implantation, further extending the presence of the pharmaceutical within the treatment window. In vitro and in vivo animal studies have demonstrated efficacy of this technique [88,99••]