

Trends in Technology of Operative Antibiotic Therapy: A Mini-Review

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1. Abstract

Bone and periprosthetic joint infections are frequent complications of orthopaedic surgeries, leading to significant morbidity and financial burden. Current standard of care involves revision surgeries and a prolonged antibiotic course, usually with mixed results. This review serves to highlight emerging technologies aimed to treat such chronic infections.

There is a need for biomaterials that maintain structural integrity as well as promoting an antibiotic-rich environment. Calcium phosphate cement infused with antibiotics has achieved moderate success due to its mechanical properties. Similarly, bioactive glasses loaded with antibiotics such as silicate and borate have the potential to transform into hydroxyapatite, providing structural support. Novel research developments include the coating of titanium implants with silver or other antimicrobial materials. This involves coating the implant with a superficial layer of antibiotic-infused hydrogel film as a drug-eluting device. Polydopamine biochemistry, polyethylene glycol brushes, and steric polymers may be used to inhibit the formation of microbial biofilms.

2. Manuscript

Bone infections continue to pose significant challenges in orthopaedic surgery. Pathologies such as chronic osteomyelitis, infection related to severe open fractures, and periprosthetic joint infection are relatively common problems that present with poor outcomes. The main suspected culprit is *Staphylococcus aureus*. Other involved microorganisms include *Streptococcus*, *Enterococcus*, and other Gram negative bacteria [1]. According to the 2017 National Joint Registry, infection is indicated as the reason for the primary revision of a total hip arthroplasty in 12% of cases and as the reason for the primary revision of a total knee arthroplasty in 16% of cases, especially within one year of the original surgery [2].

Current research reports the mortality of periprosthetic joint infection from primary total knee arthroplasty as high as 2.5% with a financial burden of \$50,000 per incidence [3]. Treating these infections may also require prolonged hospital admissions for pa-

tients and the risks associated with multiple surgeries [4].

The current standard of care for treating periprosthetic infections following total knee arthroplasty is a two-step surgical process. First, debridement and an antibiotic spacer is placed in order to locally deliver antibiotics that concentrate in the infected area. Polymethyl methacrylate (PMMA) cement is generally used to serve as a loading material for heat-stable antibiotics [5]. The antibiotics can be used in their powder form in order for prolonged and concentrated antibiotic release [6]. The spacer also retains the proper knee alignment while promoting healing. In between this primary and secondary surgery patients are typically administered intravenous antibiotics that are specific for the identified pathogen. If no pathogen can be identified due to ineffective cultures, patients are administered broad spectrum antibiotics such as vancomycin and cefepime (fourth-generation cephalosporin) [7]. There have been a multitude of studies that compared the outcomes between static and articulating; however, a recent sys-

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tematic literature review failed to detect a significant difference in the efficacy of each spacer to eliminate the periprosthetic infection [3].

Debridement, antibiotics, irrigation, and retention of the prosthesis (DAIR) may be preferred over the two-step method in acute infectious cases without many complications. This is recommended for acute cases that occur within four weeks of the operation or within two weeks of an acute hematogenous infection of the prosthetic joint.⁴

Another suggested option is to prophylactically provide patients with antibiotics. Al-Mayahi et al. [8] reported that after administration of a single dose of parenteral antibiotics, the number of intraoperative culture negatives quadrupled. This was a significant finding compared to patients who did not receive the prophylaxis. This treatment had a higher rate of antibiotic-resistant non-fermenting gram-negative rods as well as skin commensals [8]. However there are concerns over this strategy as the use of systemic antibiotics possess minimal selectivity, limited effectiveness, and carries the associated risks of general toxicity and furthering bacterial resistance [9]. Resection arthroplasty, arthrodesis, and above the knee amputation are considered last-resort measures for specific patient circumstances [6].

Other current strategies are now focusing on eliminating the need for a two-step surgical treatment due to potentially unnecessary risks of multiple procedures and secondary infection. The PMMA cement that is commonly used today must be taken out during the second surgery because it is not composed of biodegradable materials.⁵ Biodegradable substances that are used in current practice are the incorporation of collagen fleece which is successful when also administering systemic antibiotics. Depending on the fiber content of the collagen, degradation time (depending on chemical cross-linking, porosity, etc.), and the amount of collagen used, there is potential for a wide variety of uses, such as a quick and highly concentrated release of antibiotics or a more sustained release over a longer period of time [10].

Calcium sulfate beads are also biodegradable inorganic carrier materials currently on the market. Calcium sulfate hemihydrate allows incorporation of water-soluble antibiotics, which can be used to treat osteomyelitis. Its mechanism provides a time-dependent release of antibiotics as the calcium sulfate degrades [5].

Newer technologies under development also aim to proactively lessen the probability of these devastating infections. Titanium orthopaedic implants are commonly used due to its desirable endurance to corrosive loading forces and functional strength. Many researchers have attempted to coat titanium implants with antimicrobial properties.⁹ Active antimicrobial measures typical-

ly involve silver, which has non-specific properties against both Gram positive and Gram negative microorganisms [11]. Passive antimicrobial measures have described the use of polyethylene glycol (PEG) brushes as well as other steric polymers that may prevent the initial formation of devastating biofilms, which would require the administration of heavy antibiotics. Sileika et al. [12] reports a technique that can combine both active and passive antimicrobial measures. Their technique utilizes a polydopamine primer that may subsequently be used to incorporate both silver nanoparticles as well as PEG [13].

The use of polydopamine biochemistry has also been used to develop a localized drug delivery system for more specific treatment as opposed to non-specific silver nanoparticles. Polydopamine can be used to bind a vancomycin-infused hydrogel film, bound by PEG-poly(lactic-co-caprolactone) (PEG-PLC) membrane. Incorporation of cross linked starch allowed slow, sustained vancomycin release for over four weeks. This technology has the potential to prevent the very common adverse effect of implant-related infections [9].

Calcium phosphate $\text{Ca}_3(\text{PO}_4)_2$ cement infused with antibiotics are also a developmental area of interest due to this material possessing the same chemical make-up of bone, the direct placement of antibiotics into the bone, and its low temperature incorporation promotes a suitable environment for an array of antibiotics. [58] Its mechanism involves slow resorption of antibiotics through the cement.⁵ Porous hydroxyapatite (HA), $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, and beta-tricalcium phosphate (β -TCP) own a similar resorption mechanism that also incorporates impregnated granules and scaffolds. HA infused with antibiotics has been successful in treating osteomyelitis in animal models.

Bioactive glass is another area of interest due to its mechanism of transforming from glass to HA, promoting osteogenesis and a strong recovery. Silicate glass releases ions (zinc, copper, iron, etc.) that enhance anti-microbial activity but may not completely transform into HA. Borate glass is a newer compound that more completely transforms into HA. Both glasses may change the local physiological environment, be incorporated with the deposition of antimicrobial substances such as silver, and sol-gel derived glass with antibiotics [5].

Future research should focus on more biodegradable and resorbable methods to avoid complications unnecessary procedures and known side effects of current use of antibiotic spacers, such as bone loss and poor quadriceps function [6]. These new technologies can revolutionize the standard of care when faced with the difficulties of a bone infection.

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