Antibiotic-impregnated Cement Spacers for the Treatment of Periprosthetic Joint Infection

Abstract
The common treatment of chronic infection from periprosthetic joint infection is two-stage revision arthroplasty. The first-stage revision will use an antibiotic-impregnated cement spacer to maintain alignment, prevent soft tissue contracture, and produce high local drug concentration. An inadequate of antibiotic elution may cause drug resistance. There are many factors that influence the elution of antibiotic from the bone cement spacer including the type of antibiotic used, the amount of antibiotic, the type of bone cement, the porosity of bone cement, and the mixing method. The preparation of a proper and effective antibiotic-impregnated cement spacer can help the treatment of periprosthetic joint infection to be successful.

A periprosthetic joint infection after a total hip or knee arthroplasty is a serious complication for the orthopedic surgeon to resolve. It is currently one of the most common indications for total hip revision or knee arthroplasty with an estimated prevalence of between 0.5-3%. Periprosthetic joint infections divide into 4 categories which are: Type I (Early postoperative infection), Type II (Late chronic infection), Type III (Acute hematogenous infection), and Type IV (Positive intraoperative culture). The gold-standard treatment for chronic infection is a two-stage revision surgery, first described by Insall et al in 1983. The surgery methods included removal of prosthesis and cement, debridement, placement of antibiotic-impregnated cement spacer, intravenous antibiotic, and delayed second stage revision arthroplasty.

In 1958, Sir John Charnley began using bone cement on numerous patients for the fixation of joint reconstruction while the use of bone cements or polymethyl methacrylate (PMMA) began with Otto Röhm’s invention in 1901. And in 1970 Buchholz introduced the idea of adding an antibiotic to the cement to decrease the incidence of infection. Antibiotic-loaded bone cement (ALBC) has been widely used for the treatment of total joint arthroplasty ever since. ALBC was introduced by Buchholz as antibiotic-impregnated cement spacers; it has become more commonly used for the treatment of established periprosthetic joint infection (PJI). There are several advantages to ALBC which include maintaining alignment, preventing soft tissue contracture, producing high local drug concentration with fewer risks of systemic complication.

Antibiotics can elute from a cement spacer by a proportion of 1.6-11%. Del Real et al. divided antibiotic elution into three phases based on in vitro study. Thirty percent of the antibiotic was eluted in the first 10 hours (phase 1). Sixty percent of the antibiotic was eluted in the next 16 days (phase 2), and the final 10% of the antibiotic was released during the following 54 days (phase 3). Most antibiotic implants elute most of their antibiotic by 9 weeks, but they continue to diffuse at sufficient levels for months. For the best success of periprosthetic joint infection treatment, a bone cement
spacer should deliver high doses of antibiotic at the site of infection with little systemic toxicity.\textsuperscript{1,6} There are many factors that influence the elution of antibiotic from bone cement spacer as follows:

1. **Type of antibiotic:** Any antibiotic added to bone cement has to fulfill certain criteria including: its water solubility, its thermodynamic stability (to withstand the heat of cement polymerization). Furthermore, bacteria should be susceptible to the antibiotic, and the antibiotic should be suitable for local tissue release.\textsuperscript{1,6,7} The most commonly added antibiotics to bone cement are cephalosporins, gentamicin, erythromycin, clindamycin, tobramycin, daptomycin, fluoroquinolones, and vancomycin. Adams et al\textsuperscript{8} found that some antibiotics elute better than others out of the same cement type, and of these vancomycin, clindamycin, and tobramycin displayed a greater and more consistent elution profile than cefazolin and ciprofloxacin. Furthermore, Brien et al\textsuperscript{10} analyzed the vancomycin concentrations in hemovac drainages after total hip arthroplasty and noted that there was some variability in the vancomycin elution rates from the same cement types. However, with the emergence of methicillin-resistant staphylococcus aureus (MRSA) as a major pathogen, vancomycin has become the most commonly used additive to bone cement in revision joint surgery. A review of the bacteriologies of infected implants showed that 99.2% of infected implants are sensitive to vancomycin.\textsuperscript{7} In addition, an antifungal agent such as amphotericin B can also be added to bone cement for reducing fungal infection at the site of a total joint arthroplasty.\textsuperscript{1,6}

2. **Amount of antibiotic:** In general, commercially prepared antibiotic-loaded bone cement contains low doses of antibiotic (0.5-1 gram (g)) and is commonly used for prophylaxis fixation as the prophylaxis against bacterial infection. The ingredients and the mixing of bone cement are typically manufactured in the operating room. The addition of high-dose ALBC in bone cement can help to increase antibiotic elution but can also decrease bone cement strength. Lautenschlager et al\textsuperscript{11} found that the addition of 4.5 g of gentamicin powder per 40 gram package of cement decreased compression strength to below the American Society for Testing and Materials (ASTM) standard (70 MPa) due to an increase of porosity. However, the strength of a high-dose ALBC is not an important factor in the first stage of revision surgery because the antibiotic-loaded cement spacer is normally used only temporarily.\textsuperscript{2} The study of Springer et al\textsuperscript{12} revealed that the average doses of 10.5 g of vancomycin and 12.5 g of gentamicin to be clinically safe, with no evidence of adverse effects. However, it had been reported that 8 g of antibiotics per 40 g of bone cement is the highest ratio that can be introduced whilst still allowing the cement to be molded and formed\textsuperscript{13} as bone cement spacer. Moreover, it is possible for combining more than one antibiotic in bone cement spacer. The findings showed to combine vancomycin and tobramycin acted synergistically with one another and affected the bactericidal activity of vancomycin.\textsuperscript{1,6}

3. **Type of bone cement:** Different brand of bone cement also play a role in antibiotic elution. There was a study showed that antibiotics leach from Palacos bone cement in higher concentrations and for longer periods of time when compared to Simplex-P, CMW, and Sulfix acrylic bone cements.\textsuperscript{9} It described that the porosity of Palacos bone cement is higher, which increases antibiotic release compared to other types of bone cement.

4. **Porosity of bone cement:** The increase of porosity by adding space fillers can increase antibiotic elution. McLaren et al\textsuperscript{13,14} reported that the elution of antibiotic from ALBC could be increased via the use of space fillers such as xylitol, glycine, sucrose, and erythritol. Kuechle et al\textsuperscript{15} found that the addition of 25% of dextran to the cement enhanced the release of antibiotics in the first forty-eight hours up to approximately four times more when compared to a routine preparation, and increased the length of the elution to up to ten days more compared to only six days seen with a routine preparation. Moreover, the porosity can be increased by a mechanical mixer (mixing drill piece) during the manufacture of bone cement.\textsuperscript{16}

5. **Mixing method:** Lewis G\textsuperscript{17} described cement mixing methods and categorized these methods into manual or hand mixing, centrifugation, vacuum mixing, and combined mechanical mixing types. In manual or hand mixing methods, the components are normally stirred in an open bowl with a spatula at 1 Hz for between 45 and 120 seconds. The different techniques of bone cement preparation can affect the cement porosity and antibiotic elution. Macaulay et al\textsuperscript{18} noted that the percent porosity that results from hand mixing bone cement is higher than that of bone cement produced via vacuum mixing. Therefore, bone cement that is prepared by hand mixing can exhibit greater antibiotic elution. Also, there was a study that showed that the addition of antibiotic to bone cement during the dough phase (delayed antibiotic addition) could increase antibiotic elution.\textsuperscript{19}

Antibiotic-impregnated cement spacer for two-stage revision arthroplasty can be divided into 2 types which are the non-articulating (block or static) spacer and articulating (mobile) spacer. The advantages of a mobile spacer are the improvement of function prior to the second-stage reimplantation and less scar formation after resection arthroplasty. However, there is no significant distinction between static or mobile spacers for periprosthetic joint infection.\textsuperscript{1}
Systemic toxicity related to the use of antibiotic cement has rarely occurred even in cases of higher doses of antibiotic added to bone cement. The study of Duncan and Masri\(^\text{20}\) found similar safe levels even with much higher doses of tobramycin. They recorded serum tobramycin levels of < 3 mg/L despite a use of up to 3.6 g of tobramycin powder per 40 g of bone cement. However, Raaij et al.\(^\text{21}\) reported a case of acute renal failure that developed in an eighty-three-year-old woman after treatment with 2 g of gentamicin in a 240 g block of cement combined with seven chains of polymethylmethacrylate beads also impregnated with gentamicin. No local toxicity to cells at the interface of the antibiotic cement has been reported, but a few have examined changes in cell function. The study of Isefuku et al.\(^\text{22}\) noted that gentamicin levels of > 100 mg/L inhibited osteoblast proliferation in in vitro experiments. The surgeon should be aware of these potential complications.

**References**


**Conclusion**

The use of ALBC spacers is now considered to be standard care for patients with chronic infection at the site of a total joint replacement. An effective high-dose ALBC spacer can be prepared by manual or hand mixing. Also, the polymethylmethacrylate monomer and powder must first be mixed together to form the liquid cement before the antibiotic is added. The most commonly used bone cement is palacos bone cement because it contains higher porosity than other types. For the antibiotic, the most commonly used antibiotics are vancomycin and tobramycin. However, the choice of antibiotic much depends on the extent to which the bacteria is susceptible to the antibiotic.