

CURRENT CONCEPTS REVIEW

The Use of Antibiotic Impregnated Cement Spacers in the Treatment of Infected Total Joint Replacement: Challenges and Achievements

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Abstract

Two stage total hip arthroplasty revision surgery includes foreign material debridement, insertion of antibiotic impregnated cement spacer, and finally, reimplantation of the prosthesis. This review has aimed to evaluate the efficacy of antibiotic impregnated cement spacers in infection control and eradication in arthroplasties.

A total of 85 articles on total hip arthroplasty were used in this narrative literature review.

High concentrations of the antibiotic in targeted drug delivery by means of using antibiotic impregnated cement spacers is effective against infections while reduces the side effects of systemic antibiotic therapy. This results in prevention of bone and muscle atrophy as well as size discrepancy. Also, antibiotic impregnated cement spacers reduce dead space and help stabilize the limb in total hip arthroplasty. Despite all reported drawbacks, antibiotic impregnated cement spacers seem effective in eradicating infections, although a consensus has not been yet achieved.

Level of evidence: I

Keywords: Antibiotic, Cement spacer, Infection, Total joint replacement

Introduction

1. Is there any significant difference between antibiotic-impregnated cement spacers and their plain form in management of periprosthetic infections?

2. Does the articulation of antibiotic cement spacers alter their release kinetics?

3. Does manual additional antibiotic alter the mechanical strength, release kinetics and microbial resistance of antibiotic impregnated cement spacers?

4. What are the influencing factors on antibiotic release from cement spacers?

Total joint arthroplasty (TJA) is the treatment of choice for relieving arthralgia and amendment of mobility loss resulting from severe osteoarthritis or

other arthropathies. Despite very good or excellent clinical outcomes, there is still a small but important risk of serious complications associated with these procedures (1, 2). Periprosthetic joint infection (PJI) is one of the most devastating and costly complications following TJA (3). Using the nation-wide in-patient sample (NIS) data, Kurtz *et al.* found the relative incidence ranged between 2.0% and 2.4% of total hip arthroplasties (THA) and total knee arthroplasties (TKA) (4).

Nowadays, the management of periprosthetic joint infections is equally focused on the eradication of the infection and the preservation of a functional joint all through the treatment's period. An early postoperative

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infection or an acute hematogenous infection may be amenable to a debridement and implant retention procedure, while two-stage arthroplasty exchange would be preferable for late chronic infection (5). Once the infected implant is removed, debridement and substitution of necrotic and granulation tissue with antibiotic impregnated cement articulating or static spacers is a standard interim therapy to improve the outcome of re-implantation and prevent recurrence of the infection.

Antibiotic loaded cement spacers could offer a higher success rate of infection's control due to increased local concentration of antibacterial agents with minimal effects on serum or urine antibiotic levels (6-8). Apart from that, these spacers maintain joint space and stability (9). Local delivery provides substantially high concentrations of the antibiotic at the site of poorly vascularized infected bone which is inaccessible from even high doses of systemic intravenous antibiotics (10-13).

The rate of therapeutic success as defined by the eradication of the periprosthetic infection with the use of antibiotic loaded cement spacers has been reported over 90% (14). However, despite their proven advantages, antibiotic cements are associated with some potential drawbacks, which should be taken into consideration by the treating physician. Controversies still exist regarding the optimal dose, the type of antibiotic, the category of periprosthetic infection that should be used and the type of cemented spacer (15).

The two-stage revision process allows for biofilm disruption in multiple theoretical ways. Higher local concentration of antimicrobial, combination of antimicrobial therapy, sustained concentrations of antibiotics, and hardware removal with tissue debridement are all strategies in biofilm elimination (16).

Basics in periprosthetic infection

The treatment protocol for infected THA/TKA patients depends on the severity and duration of the infection and the stability of the prosthesis (17). A two-stage implantation is mostly preferred in patients with chronic infection and loose implants (18).

The standard classification of infections at the site of total joint arthroplasties based on the timing of the surgery and the source of infection includes the following types:

- Acute postoperative infections (both superficial and deep) occur within 4-6 weeks after implantation, while wound infections occur within the first 4 weeks after the surgery. Patients should be managed with surgical debridement, implant retention, possible replacement of the mobile parts of the prostheses (polyethylene, femoral head) and intravenous antibiotic therapy (19).

- Chronic infections have delayed presentations, usually 4 weeks after the operation. Worsening pain and aseptic loosening will be treated with a two-stage revision surgery (20).

- Acute hematogenous infection is a rare complication which might occur within the first weeks after a joint replacement surgery (19). Debridement with retention of

the stable prosthesis along with intravenous antibiotics is the treatments of choice. Positive intraoperative cultures, in which a patient undergoing revision for presumed aseptic failure is found to have a positive intraoperative culture. Some patients falling into this category do not truly have PJI (21). A course of antibiotics is recommended.

The incidence of post-TJA infections has been reduced to 0.3%-2% in modern operating rooms which are mostly equipped with laminar airflow, body exhaust suits, high airflow, and ultraviolet lights (10, 22, 23). The rate of infection after revisions is higher than primary TJA, especially in TKA (24, 25). In a two-stage surgery, first of all the surgeon radically removes the whole prosthetic components, infected tissue and bones. Then, the therapeutic regime is included of a local antibiotic delivery via cement spacers conjugated with systemic antibiotics (26).

The use of antibiotic impregnated cements in periprosthetic infection

Antibiotic loaded acrylic bone cement was firstly introduced as a therapeutic choice for preventing infection in patients undergoing TJA by Buchholz and Engelbrecht (27). Since then, it has gained increased popularity amongst physicians in the forms of spacers or beads in revision arthroplasties. Indeed, antibiotic impregnated cements are much more common in two-stage procedures rather than in primary TJA, where they could be possibly used for infection prophylaxis.

Two-stage revision surgeries for the treatment of periprosthetic joint infection are associated with prolonged hospitalization, loss of joint function, increased cost, and increased perioperative morbidity. Despite favorable outcomes of both one- and two-stage surgeries, two-stage revision surgery has been considered as the gold standard for chronic infections (28). In addition, the use of antibiotic-cement-only prosthetic components has led to improved outcomes in terms of postoperative range of motion and pain when compared with antibiotic-cement-covered prosthetic components (29, 30). Antibiotic loaded cement spacers are usually recommended for two types of periprosthetic infections: the late chronic and the acute hematogenous infections. The first stage of treatment includes explantation of the loose prosthesis, debridement of the soft and bony tissue, and insertion of an antibiotic impregnated cement spacer. The reimplantation will be performed after full eradication of infection (28). Two-stage revision arthroplasty can also be performed without the use of spacers, a fact that allows complete removal of foreign material; however, reimplantation during the second stage operation will be more difficult due to arthrofibrosis and loss of tissue planes (31).

The combination of systemic antibiotic therapy based on the positive intra-articular cultures with a locally acted antibiotic-loaded cement spacer aims to completely eradicate infection, stabilize soft tissues, simplify the reimplantation, and reduce bone loss between the two stages (32, 33). Although the use of

antibiotic impregnated cements is an effective strategy for the management of periprosthetic infection when combined with the proper systematic antibiotic treatment, some authors have suggested that, they should be mostly limited to cases of deep surgical site infections, patients with diabetes mellitus, or immunosuppression (34).

A meta-analysis study by Garvin et al. in 1995 on revision of infected hip arthroplasties showed significantly better rate of success in antibiotic loaded group for both one- and two-stage procedures, with a total 82% (976 of 1189 joints) and 91% (385 of 423 joints) successful infection eradication, respectively (35).

As the surface morphology of AIBCs provides colonization, enhancement of the manifestations of antibiotic-resistant microorganisms is a concern. Also, prolonged exposure to antibiotics in sub-inhibitory levels can cause mutational resistance (36). An in vitro animal model study by Thomes et al. showed that a lower overall rate of infection was seen in the gentamicin-loaded cement group in comparison with saline as a control group, but there was a significantly higher rate of gentamicin-resistant infection in this group ($P < 0.01$). According to them, the antibiotic-impregnated cement had an optimum surface for colonization, whereas prolonged exposure to antibiotic allows mutational resistance to that specific antibiotic (37). Hope et al. reported a significant relapse of infection with the use of gentamicin-containing cement in the primary arthroplasty with the emergence of gentamicin-resistant coagulase-negative staphylococci (C-NS) (38).

The addition of antibiotics: type and dosage

A systematic review by Block and Stubbs was conducted in order to investigate whether the combination of antibiotics in cements has a therapeutic effect or not (39). The whole validated randomized and non-randomized clinical trials were included according to pre-determined criteria. From the nine randomized controlled trials (RCTs), which were included in their review, Block and Stubbs documented that, the difference between plain and antibiotic cement groups was not significant in four studies, while in another five trials antibiotic impregnated cements were associated with statistically significant reduction in the frequency of deep infection (39).

The success rate of eradicating infections using ABLC (Antibiotic Loaded Cement) spacer ranges from 88-100%. This achievement could result in shorter hospital stay, decreased costs, increased function and mobility, higher patient satisfaction, and decreased pain (25).

Local delivery of antibiotic via bone cement allows for a direct route of action, bypassing the need of adequate blood flow to reach the target tissue. Also, infection sites can have zones of avascularity with biofilm formation, making systemic antibiotic penetration to local infection challenging without using toxic doses (16).

Systemic antibiotics have a known risk of renal injuries, aminoglycosides via tubular cell toxicity, and vancomycin via acute interstitial nephritis. As with most adverse

drug reactions, risk of renal injuries rises with increasing dose and pre-existing renal abnormalities or disease (40).

Antibiotics incorporated in bone cements should be of broad-spectrum, covering both Gram-negative and Gram-positive pathogens. Liquid antibiotics are not preferred due to their possible catalyst dilution effect on cement polymerization (41). Low sensitizing potential, low protein-binding, chemical and thermal stability, water solubility, and minimal stimulation of resistant reactions are necessary for the therapeutic efficacy of the loaded antibiotic and the integrity of the cement spacer. Gradual sustained release of the antibacterial drug over time is essential for a long-lasting therapeutic effect (35). The bacterial growth in prosthetic infections is suspended in planktonic state and biofilm; however, the germs can reactivate when the antibiotic level decreases to sub-inhibitory level (42).

The molecular size of the drug seems to be of paramount importance. Smaller molecules have a much higher water solubility, which leads to rapid reduction in inhibition zones of the cements (43). The antibiotic should be added when the cement is ready (25).

The optimum antibiotic-to-cement ratio has been suggested to be 10-15 % (weight/weight) in order to keep the antibiotic level higher than the minimum inhibitory concentration at the spacer-body interface for 6 weeks (9, 44). The more the antibiotic concentration is, the less the mechanical features are expected to be (22). The highest suggested antibiotic-to-bone cement proportion is 8/40 (weight/weight) (45).

Considering the type of microorganism and the specific conditions of the patient, the choice of antibiotic agent is tailored for different patients. *Staphylococcus* species are the most prevalent bacteria in infected TJAs (46). The success rate will increase if the susceptibility pattern is known and the appropriate cement is available. As methicillin-resistant *Staphylococcus aureus* (MRSA) induced infection is a clinical complication with high treatment failure rate, antibiotic cement spacers must be capable of eradicating MRSA (17, 47). Commercial cement spacers with broad spectrum antibiotic are usually used to suppress the most frequent microorganisms (48). Tobramycin, gentamycin and vancomycin are the most commonly used and studied antibiotics in cements. With the rise of methicillin- and vancomycin-resistance, optimum alternatives like daptomycin or tobramycin has been introduced (15). The mechanical features of the bone cement loaded with a combination of daptomycin and tobramycin have been reported to remain unaffected. There is no consensus that the benefits of antibiotic loaded cements outweigh the promoting resistant microorganisms. To the best of our knowledge, clinical studies on some antibiotics capable of loading in cement spacers (teikoplanin, cephalosporines, piperacillin, and tazobactam) are scarce (49).

The antibiotic-to-cement ratio depends on whether it is used as spacer or for fixation; however, the mechanical properties of the antibiotic loaded cement may be affected by the ratio (10, 50). Currently, the addition

of large antibiotic doses is intended to increase the antibiotic elution rate from the cement. However it leads to a reduction in mechanical strength. When antibiotic cements are used as temporary spacers, this factor loses its importance unlike release kinetics which matters. High amounts of antibiotic should be eluted in first hours after implantation.

An in vitro study investigated the action of three different antibiotic-loaded cements (daptomycin, vancomycin, and teicoplanin) against methicillin-susceptible, methicillin-resistant, and vancomycin-intermediate strains of *Staphylococcus aureus* (51). While all three antibiotics maintained their antibacterial activities, teicoplanin-loaded cement depicted better elution and a longer inhibitory interval, and vancomycin impregnated cement showed a 21-day antibacterial effect (51).

In another study, the ten-day elution test illustrated larger inhibition zones by adding fosfomycin to Palacos® cement (containing 0.8 g gentamicin and 0.5 g gentamicin sulfate) (Smith & Nephew, USA) than to using Palacos® only (52). This study was designed to investigate the increasing elution effect of dextran fluid during the mixing phase in four different fosfomycin, gentamicin, clindamycin, and vancomycin loaded cement groups.

Meropenem has been reported to elute in measurable pharmacologic concentrations from the cement, remaining active against MRSA, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumonia* for a 3-27 days period (53). Combining two antibiotics has been shown to be superior than a single antibiotic in both laboratory and clinical settings (54). Interestingly, the combination of meropenem and vancomycin is broad-spectrum and enhances vancomycin elution (55).

A different study by Koo et al. with 2g of cefotaxime per 40g of cement along with vancomycin and gentamicin on 22 patients with infected THA resulted in 95% infection-free rate at the end of a 41 months follow-up.

Vancomycin covers MRSA while gentamicin covers *enterobacteriaceae* and *Pseudomonas aeruginosa* (54, 56). According to Park et al, a combination of 4.5 g piperacilin/tazobactam with 2 g vancomycin in cement spacers has been resulted in the infection's eradication in 32 out of 36 patients treated (57).

Although ciprofloxacin has illustrated the minimum inhibitory elution concentrations for common microorganisms associated with osteomyelitis for up to 24 days, it may inhibit bone, ligament, and soft-tissue healing (58).

Table 1 summarizes a list of available antibiotics commonly used in spacer cements.

When we tried to isolate and exclude the therapeutic effect of systematic antibiotics which were used for the treatment of deep joint infection and focus only on the actual efficacy of local delivery of drugs through antibacterial-loaded cement spacers, the literature data existed were insufficient. Future prospective randomized clinical trials are required to compare the therapeutic value of the combined systematic antibiotics and

antibiotic-loaded spacers versus systematic antibiotics alone (or versus systematic antibiotics and cement spacers without any loaded antibiotic).

The type of cement materials

Poly(methyl methacrylate) (PMMA) has been used as a carrier for local antibiotic therapy, due to its ability to elute antibiotics. There are several types of acrylic bone cements, either premixed with antibiotics by the manufacturer or added by the surgeon in the operating room. PMMA cements contain two powder and liquid phases. The powder phase is almost the same in different clinically used brands and includes polymethylmethacrylate, methylmethacrylate, methacrylate, and styrene along with barium sulfate, zirconium dioxide, and benzoil peroxide and also gentamycine sulfate, colistimethate sodium, and erythromycin. The liquid phase consists of methylmethacrylate and N,N-dimethyl-p-toluidine. Despite the usage as a gold standard in medical applications, tissue necrosis, vasodilation, and even heart attack are some of the risks of PMMA (59). Leakage of residual toxic monomers from the polymerization process into the bloodstream and

Table 1. Frequently used antibiotics for the purpose of addition into bone cements with their attributed weigh proportion per 40 g of the bone cement (low dose/high dose) (10)

Antibiotic	Low dose (g/40 g cement)	High dose (g/40 g cement)
Amikacin	1	2
Amphotericin B	0.2	
Cefotaxime	2	3
Ciprofloxacin	0.2	3
Clindamycin	1-2	4, 8
Cefazolin	1-2	4-8
Cefuroxime	1.5	3
Colistin	0.24	
Daptomycin	2	
Erythromycin	0.5	1
amphotericin	0.2	
Gentamicin	0.25-1	4.8
Linezolid	1.2	
Meropenem	0.5	4
Piperacillin/Tazobactam	4	8
Tobramycin	1.2	2.4-9.6
Teicoplanin/tazobactam	0.5	
Vancomycin	1	3-9

suspected carcinogenesis are possible complications.

Other types of materials like calcium phosphate and calcium sulfate have drawn attention in laboratory settings; however, their clinical use is still limited due to poor mechanical strength (60). Incorporation of vancomycin and gentamycin into Callos[®], a calcium phosphate cement, increased its setting time from 4 minutes in antibiotic-free samples to 10 and 20 minutes, respectively (61). The addition of antibiotics depicted minimal effect on the handling behavior of the cement. The kinetics of transformation into poorly crystalline apatite was unaffected by the addition of antibiotics, while it showed a sustained 21 days release of antibiotic in phosphate buffered saline as well as greater inhibition zones until 7 day (61).

Articulating or non-articulating

Based on the mobility limitation spacers are classified into articulating and non-articulating. From the antibiotic release point of view, non-articulating spacers are capable of locally releasing of high concentrations of antibiotic, improving patient autonomy, and joint space maintenance for further stages. A narrow line between bacterial susceptibility and resistance development should be preserved in both articulating and non-articulating spacers, while greater intra-articular levels could be delivered through a parenteral route (62, 63). Better preservation of bone mass, more efficacious eradication of infection, preventing of extensor mechanism impairment, and possibility of adding high doses of antibiotic are some of the advantages of an articulating system compared to a non-articulating one (57, 64, 65).

Articulating spacers are preferred for patients whose spacers have to be in place longer than 3 months. Also, in cases of large bone defects, ligament instability and/or defects of the extensor mechanism are not ideal preconditions to implant an articulating cement spacer (14). There is also a decrease in bone loss when an articulating spacer is used versus a static spacer or no spacer. The space-occupying and articulation aspects of the cement spacer account for the prevention of negative outcomes described above. The other major benefits comes from the addition of antibiotics into the cement (40).

In a retrospective cohort study conducted by Hsieh et al. in a mean duration of about 5 years on patients with deep infection at the site of hip implant, patients either had antibiotic cement beads or antibiotic cement spacers inserted into the hip joint after removing previous prosthesis. They also were treated with systemic antibiotics. These oral antibiotics and intravenous drugs were given for two to six weeks. The overall rate of infection control was similar between groups (94% versus 97% in the bead and spacer groups, respectively, $P=0.69$). Two of bead group and one of the spacer group could not have a joint re-implanted due to continuing infection. Persistence of infection following the first stage surgery was associated with inadequate debridement and immunocompromised state (66).

Antibiotic Release from cement

The drug elution's behavior is variable according to the type of antibiotic and cement, and the mixing conditions (62). The antibiotic is initially released from the surface of the cement, but continues through a network of cracks, voids, and cavities produced during abrasion (67). Any increase in the surface area will increase the elution of the antibiotic (68). Vacuum mixing improves the mechanical features of the cement through decreasing the porosity and hence, decreases the rate of fractures during cyclic loading (10, 69, 70). Hand-mixed cement is associated with a decreased release of antibiotics, whereas vacuum-mixing would result in only a minor reduction in antibiotic release, and according to some previous results, vacuum-mixed bone cements have a better in vitro fatigue performance than hand mixed cements (71, 72). Hand-mixed antibiotics are not homogeneously distributed in the cement, so the elution rate decreases. As porosity increases the elution rate, intact crystals left from mixing process create a more porous cement with higher release rate.

However these partially mixed cements are not suitable for prosthesis fixation due to their weak mechanical strength (73). Dextran has been used as a porosityizer to increase the elution rate. Antibiotic release from Dextran-containing samples is four times more than the routine samples within the first 48 hours. Besides, the duration of elution was extended from 6 to 10 days (74).

The release kinetics of the different antibiotics from cement varied widely (62, 75). The majority of the relevant studies support that the antibiotic release occurs within the first postoperative days (mostly in the first 24 hours), while few authors have reported that the release lasts for many days (36, 76, 77). Type and concentration of the antibiotic as well as the composition, surface morphology, and porosity of the cement are factors influencing the release rate.

Vancomycin-impregnated cement spacers have shown remarkably better and longer inhibitory effects on MRSA, when compared with fosfomycin-loaded cement spacers (17).

In Vitro tests, such as disk diffusion bioassay, actually have some limitations to show a large inhibitory zone in a high concentration of highly soluble antibiotic.

Bertazzoni Minelli et al. evaluated the delivery of gentamycin and vancomycin from PMMA spacers before and after implantation of total hip replacement in a clinical series of 20 patients (78). This was achieved by implanting 20 commercial spacers immersed in phosphate buffered saline at 37°C for 10 days. Commercial spacers containing 1.9% gentamicin were drilled and the holes were filled with PMMA cement mixed with 2.5% vancomycin before implantation. The antibiotic concentrations in explanted spacers were measured 3-6 months later. Gentamicin and vancomycin release ranges were reported as 0.05%-0.4% and 0.8%-3.3%, respectively. Both drugs showed high initial release and reduced constant secondary elution kinetics during several months. Incorporation of vancomycin into the surface of the spacers permitted

spacers to be prepared with multiple antibiotics present and without adversely affecting the release kinetics of the agents (78).

In a different study, the release of gentamicin and vancomycin from antibiotic impregnated hip spacers and the bacterial growth inhibition in both in-vitro and in-vivo conditions were evaluated. The synergic effect of aminoglycosid-glycopeptid hybrid is intended to prevent the development of bacterial resistance. However, a higher proportion of vancomycin should be used due to its higher release kinetics (79). The results illustrated higher elution rates for vancomycin and less in vivo antibiotic concentrations than in vitro. In this in-vitro study, microbial inhibition by spacers was observed for 2 weeks independently of implantation duration. Elution rates reached their peaks after 2-3 days, reduced constantly in the following 10-12 days and then dropped into sub-therapeutic levels. Bacterial inhibition lasted for around 14-30 days after the explantation of the spacers (79).

Safety issues

Despite the well-proven safety of antibiotic impregnated cements, unusual cases of related complications have to be considered in clinical applications. Table 2 summarizes the cement/antibiotic formulations along with their complications reported by some of previous studies.

While up to 2 g antibiotic per 40 g of cement is defined as low-dose and higher amounts are categorized as high-dose antibiotic cements, some studies define low and high-dose as ≤ 1 g and >3.6 g powdered antibacterial per 40 g of cement, respectively (62). No noticeable evidences of systemic toxicity or allergic reactions have been reported with the use of low-dose antibiotic cements, at least partially because gentamicin has low incidence of sensitizing reactions.

Soares et al suggested that vancomycin should not be used for prophylaxis but rather reserved for treatment of periprosthetic infections (15). Fehring et al. used 1.2 g of tobramycin and followed for 24-36 months a group of patients who received static spacers for 24-72 month

and a second group treated with articulating spacers. Three out of 25 patients of the static spacer group had reinfection, whereas one out of 15 patients in mobile spacer group had persistent drainage after the implant removal and needed arthrodesis (20).

Considering the reduced side effects compared to systemic antibiotic therapy; targeted delivery of high concentrations of the antibiotic; prevention of bone and muscle atrophy as well as size discrepancy, and despite all reported drawbacks, antibiotic impregnated cement spacers seem effective in eradicating infections, although a consensus has not been yet achieved.

Antibiotic impregnated cement spacers reduce mechanical dead space and help stabilize the limb in THA.

When articulated and non-articulated cement spacers are compared, the later one reduces the range of motion; increases the chance of size discrepancy and early loosening; causes unsatisfactory antibiotic release, and results in capsular scarring and shortening as well as additional bone loss [Table 3].

Further randomized clinical trials are needed to elucidate the efficacy of antibiotic impregnated cement spacers.

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Table 2. Cement/antibiotic formulations with their corresponding complications

Study	No. of Patient	Cement/Antibiotic Formulation	Complications
Jung et al.	82 (hip spacers)	0.5 g gentamicin and 2 g vancomycin / 40 g cement	5 cases of acute renal failure (80).
Hsieh et al.	42 (hip spacers)	480 mg liquid gentamicin + 3 g vancomycin / 40 g of cement	0.5 mg/DL increase in serum creatinine (81).
Springer et al.	36 knees 34 patients	10.5g vancomycin + 12.5 g gentamicin / 40 g cement	no complications reported (13).
Dovas et al.	a 61-year-old patient	high-dose gentamicin-vancomycin impregnated cement	acute renal failure (82).
Evans et al.	44 (total 54 periprosthetic infections)	4 g vancomycin + 4.6 g tobramycin / 40 cement	no complications reported (29).

Table 3. Examples of using various antibiotic impregnated bone cements

Study	No of patients, level of evidence	Method	Results
Goldstein et al.	5, 4	Used heavy aluminum foil in the form of osseous anatomy and hand-molded cement around it to avoid interdigitation, and a layer of sterile lubricant in between for easy removal of the foil. They used trial tibial insert for molding femoral condyles (83).	Success in five patients.
Barrack	18, 4	Used cost-effective rush pin technique for temporary hand-made antibiotic impregnated cement prosthesis for infected total hip arthroplasty (32).	The whole 12 patients presented no fractures, dislocations or infections at a two-year postoperative follow-up.
Wentworth et al.	116, 4	Reported a success rate of 83% in patients treated with antibiotic acrylic cement spacers (consisted a cemented acetabular component, with a metal endoskeleton, a femoral head, and a centralizer that are inserted into a mold and filled with antibiotic cement to create the implant) for hip replacement (84).	No growth of any microorganism was observed when samples from the operative site were cultured.
Durbhakula et al.	24, 4	Used vacuum-injected silicone molds as a cost-effective device for molding femoral and tibial components of a knee antibiotic impregnated cement spacer (33).	The infection eradication rate was reported as 92%.
Haddad et al.	41, 4	treatment with prosthesis of antibiotic loaded acrylic cement (85).	The infection eradication rate was reported as 91% in a 48 months follow-up for patients receiving knee spacers.
Hofmann et al.	50, 4	Used 4.8 g tobramycin per 40 g PMMA cement as articulating spacers created intraoperatively in TKA patients (20).	Only six patients had reinfection after 37 months follow-up and the rest presented good results.

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