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Chapter 25

Articulating Spacers in Infection of Total Knee Arthroplasty — State of the Art

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1. Introduction

Infection is one of the most devastating complications of total knee arthroplasty. It is also the leading cause of early revision after knee arthroplasty, ahead of instability and aseptic loosening [1].

Treatment of an infected total knee arthroplasty requires 3 to 6 times more hospital resources than a primary arthroplasty and 2 times more than an aseptic revision [2]. The goal of treatment is to eradicate infection and maintain joint function.

Two-stage exchange remains the treatment of choice in cases of late infection, with good or excellent results in 80% to 100% of cases; nevertheless, it is aggressive, costly, and long. It is also considered the treatment of choice in cases of fungal infection, infection by virulent organisms, inflammatory diseases, immunosuppression, and reinfection after reimplantation.

Compared with direct replacement, 2-stage revision of infected arthroplasty has several disadvantages: longer hospital stay, higher cost, longer surgical time, tissue retraction, instability, and functional limitation between procedures. From a technical standpoint, surgical reimplantation may be hampered by retraction of soft tissue and loss of tissue planes.

Most authors agree that almost all of these problems can be minimized using antibiotic-loaded articulating cement spacers, although 2-stage exchange can be used to eradicate infection both with and without cement spacers.

The most consistent results have been published with 2-stage exchange, regardless of variations in the type of spacer, causal microorganism, or duration of infection. In a systematic

review of the literature between 1980 and 2005, Jämsen et al. [3] found 31 original articles describing the results of 154 direct exchanges and 926 2-stage exchanges. Eradication rates were 73%-100% for 1-stage exchange and 82%-100% for 2-stage exchange. Final range of motion and reinfection rates were lower in the series that used antibiotic-loaded articulating spacers. No correlation was observed with the type of spacer or functional outcome between direct revision and 2-stage exchange.

2. Spacer types: Nonarticulating and articulating

The 2-stage exchange protocol was designed by Insall in 1983. Since the first report in 1990, long-term results have shown two-stage exchange to be the treatment of choice for infection after total knee arthroplasty [4]. The outcome of the original procedure was poor to fair in 20% of cases, mainly owing to functional disability and retraction of soft tissue. Atrophy, stiffness, bone loss, and increased extensile exposure were observed at reimplantation.

The use of antibiotic-loaded articulating spacers helped to reduce these complications and improve the possibilities of eradicating infection [5-9]. The choice of spacer depends on many factors, including degree of bone loss, state of the soft tissue, choice of antibiotics, and financial and technical restraints. A benefit that is common to both articulating and nonarticulating antibiotic-loaded spacers is the fact that greater intra-articular levels of antibiotic can be delivered than with parenteral antibiotics [10-11].

The approach aims to be above breakpoint sensitivity (ie, the level of antibiotic that sets the boundary between bacterial susceptibility and the development of resistance) and to eradicate infection.

Nonarticulating spacers enable local administration of a high concentration of antibiotic, improve patient autonomy, facilitate outpatient treatment, and maintain the joint space for future procedures.

Borden and Gearen [5], Booth and Lotke [7], and Cohen et al. [12] reported data for antibiotic-loaded beads and cement spacers, which are molded to adapt to the defect created by removal of the infected prosthesis. Although in some cases these authors made the spacer in 2 semi-blocks, thus forming a partial joint, neither the design of the blocks nor the rehabilitation protocol included controlled mobility. Calton et al. [9] modified this approach, although disadvantages were still observed (eg, bone loss when the spacer sank into the tibia).

Other disadvantages of this system are the minimal range of motion of the joint, which can lead to shortening of the quadriceps, capsule, and ligaments, thus increasing the need for extensile approaches with longer surgical time during reimplantation.

Antibiotic-loaded articulating cement spacers can improve function between operations and facilitate the second stage.

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Although this approach remains open to debate, most authors agree that articulating spacers provides better functional results and enable more efficacious eradication of infection than nonarticulating spacers [3], [13-15].

The shape and features of articulating spacers vary considerably, from fully manual spacers made in preformed molds to modular spacers, which include plastic and metal surfaces. Spacers differ in price, complexity, and degree of constraint. The advantages of articulating spacers are as follows: retraction of soft tissue and extensor mechanisms is prevented, high doses of antibiotics can be added in the time between operations, bone mass is preserved better than with nonarticulating spacers[9], [16], the need for expanded approaches at reimplantation is reduced, and the success rate is increased. These approaches also enable greater controlled mobility of the joint and application of a partial support brace, thus facilitating acceptable function between procedures.

3. Historical development of articulating spacers

Use of antibiotic-loaded articulating spacers was first reported by Wilde and Ruth [6] in 1988. This was the first attempt to reduce complications due to functional disability between operations, as observed in the initial work by Windsor and Insall [4].

Preformed articulating systems (PROSTALAC®) first appeared in 1992. Their main advantage was excellent tolerability and function between procedures, thanks to high joint congruence and reduced friction [17]. Their disadvantages include high cost, presence of metal and plastic surfaces that could facilitate bacterial growth, and size limitations. Preformed articulating systems are not widely used because of their price and the theoretical risk that the presence of metal and plastic components facilitates persistence of infection, although this has not been confirmed in clinical practice. Therefore, other factors (eg, aggressiveness of the microorganism, addition of high proportions of cement, and antibiotic treatment) may be more important than the type of spacer used.

Hand-made cement articulating spacers, however, maintain almost all the advantages of preformed spacers, although they also have a series of drawbacks.

Between these extremes, many authors have developed modifications to minimize the disadvantages of hand-made spacers and PROSTALAC® spacers, by adapting them to their technical and economic possibilities. The real impact of the theoretical advantages of the different types of spacer is unknown.

The main forms are as follows:

1. Manual construction of a spacer with cement in the operating room by recreating the normal anatomy of the patient [18], [19] (Figure 1) or more congruent systems (ball and socket) [20] (Figure 2).
2. Construction of customized spacers in the operating room using prefabricated silicone or aluminum molds [21], [22], or using trial components to shape the spacer [23]. Cement

molds can be made during surgery using trial components, and the definitive spacer can be made using these cement molds [24], [25].

3. Prefabricated spacers made of cement only [26].
4. Cement components in combination with modular components made of plastic and metal (PROSTALAC®, DePuy, Warsaw, Indiana) [27], [28].
5. Resterilization of the prosthesis and insertion of a femoral component and a tibial polyethylene insert with cement or a new prosthesis as a spacer (prosthesis-spacer) with high antibiotic loads [29], [30].
6. Combinations of these approaches for moderate or massive defects [31], [32].

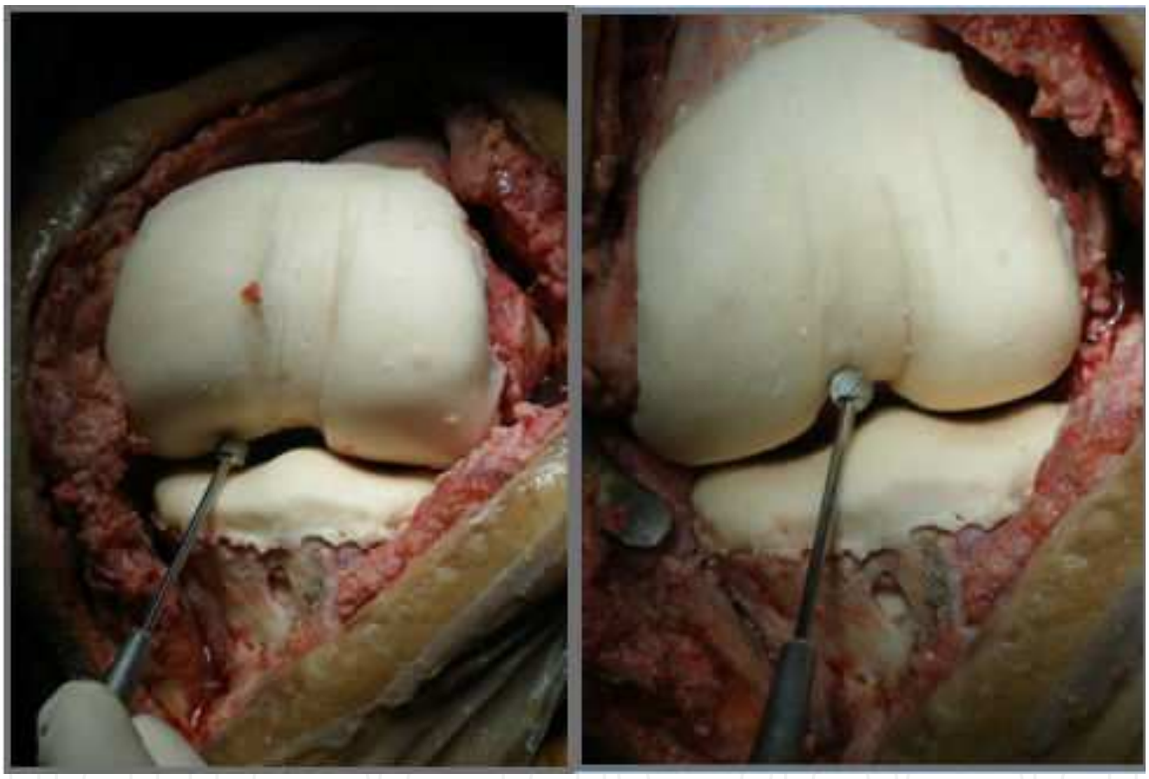

Figure 1. Remodeling prominent areas of a hand-made spacer with a high-speed burr.

Favorable results have been reported with each of these types of spacers. The more rudimentary a spacer is, the lower its congruence and the greater the sensation of popping, giving way, or instability. In contrast, it is cheaper, more widely available, and versatile. The specific advantage of spacers built manually with cement only is that the whole spacer is loaded with antibiotics, and these can be tailored to the causative organism. The spacer does not include plastic, metal, or resterilized parts and can be applied in any operating room with no need for specific instruments. The main disadvantage of cement spacers is the lack of optimal congruence, instability, and the difficulty in modeling, especially with high antibiotic loads (>10%-15%) (Figure3). In addition, cement-on-cement spacers can cause more inflammatory

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reactions as a result of particle generation; however, this has not been considered a real problem in published series [18], [21], [24].

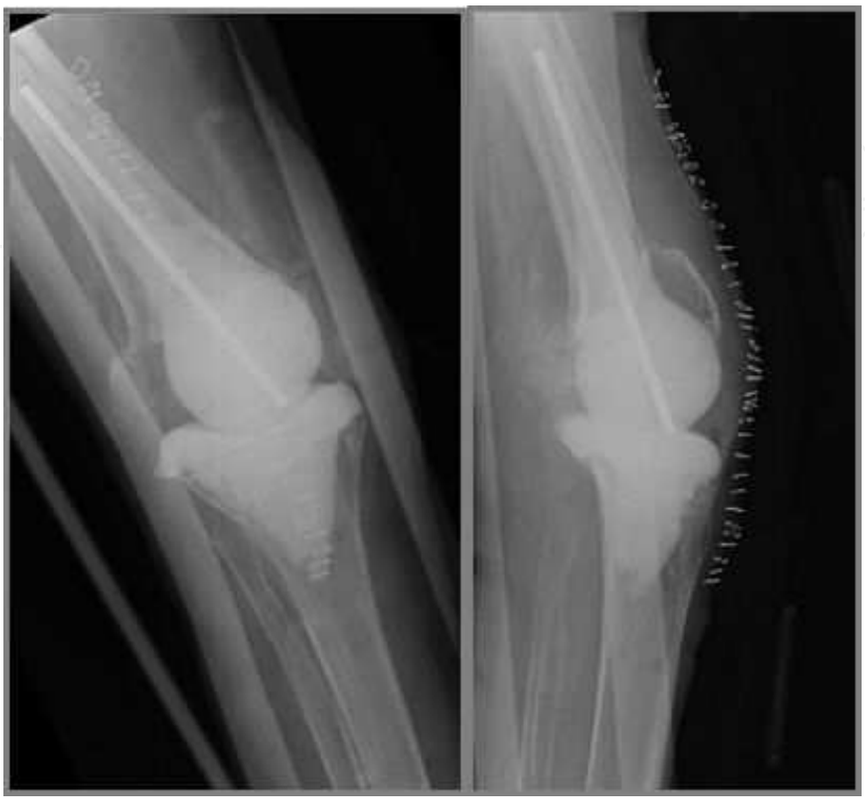

Figure 2. Ball and socket spacer.

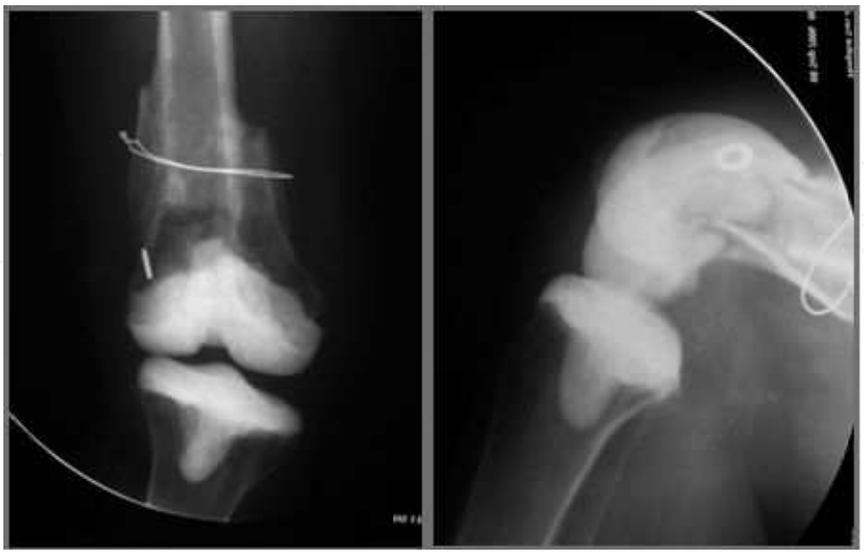

Figure 3. Hand-made spacer for a segmental defect. Excellent range of motion. Due to instability or giving way the patients usually walks with a brace.

Customized spacers constructed completely of cement using prefabricated silicone or aluminum molds are not difficult to shape with greater antibiotic loads.

By contrast, preformed spacers including metal or plastic elements or resterilized prostheses have a limited antibiotic load, which is not tailored to the patient. These spacers involve the insertion of foreign material into a septic environment. In these cases, only the cement fixing the metal components, the prosthesis, or the preformed spacer takes the maximum load of tailored antibiotics.

Also important is the degree of constriction of the spacer. All spacers made intraoperatively with a mold design lack a tibial post and femoral bar; at most, they have a tibial post that gives them some medial-lateral stability. The bar, or lever, which provides anteroposterior stability, is exclusive to PROSTALAC® systems or prosthesis-spacers.

4. Characteristics of antibiotic-loaded spacers

Elution of antibiotics from bone cement depends on several factors: the type of antibiotic, the concentration and combination of antibiotics, the porosity and type of the cement, and the surface of the spacer [33], [34].

4.1. Cement type: Commercially available vs. custom antibiotic-loaded cement

Most commercially available antibiotic-loaded cements, have a low dose of antibiotic, which can act as prophylaxis in patients at risk (ie, double prophylaxis in combination with parenteral antibiotics), or during reimplantation in a 2-stage revision of an infected total knee arthroplasty, but not for the treatment of infection when it is diagnosed[35].

Therefore, surgeons should add antibiotics to the cement to achieve the appropriate doses needed for the treatment of periprosthetic joint infection and to tailor the drug to the causative microorganism.

In comparison with commercial presentations, manually mixed cement releases less antibiotic [33], [34].

Manual mixing of cement and antibiotics increases the porosity of the cement. In theory, this approach weakens the cement, but increases the elution surface, since the antibiotic is released from the surface of the spacer and from cracks in the surface. On the other hand, distribution is not homogeneous (unlike commercially available preloaded cements), thus decreasing the rate of elution from a given surface [36], [37]. One study showed that increasing the surface area of bone cement by 40% yielded a 20% increase in the elution rate of vancomycin [38].

The addition of dextran increases porosity and elution rates. Kuechle et al. [39] noted that when dextran was added at 25%, the release of antibiotics during the first 48 hours was about 4 times greater, and the duration of elution reached 10 days instead of only 6, compared with the routine preparation. The same effect was observed with the addition of lactose and xylitol (or other sugars), which increase the release of daptomycin, vancomycin, and gentamicin [33].

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Vacuum mixing decreases the porosity of the cement and thus potentially decreases the elution rate. However, this is not true for all cements, because other factors, such as hydrophilicity or viscosity, may be more important than the area of elution.

In a recent study, Meyer et al. [34] compared the elution of 6 commercially available vacuum-mixed and manually mixed antibiotic-loaded cements. All showed detectable antimicrobial activity during the 5 days of the trial, with peak activity on the first day and levels above breakpoint sensitivity. Levels decreased rapidly thereafter. Cumulative antimicrobial activity during the trial was similar with the manually mixed Cemex Genta and the vacuum-mixed Cobalt G-HV and Palacos RG and higher than that of VersaBond AB, Simplex P with Tobramycin, and SmartSet GMV. The cumulative antimicrobial activity of manually mixed Cemex Genta over 5 days was significantly higher than that of Cobalt G-HV and Palacos RG, which in turn significantly higher cumulative antimicrobial activity than VersaBond AB, Simplex P with Tobramycin, and SmartSet GMV. Vacuum mixing increased the cumulative antimicrobial activity of Cobalt G-HV, Palacos RG, and Simplex P with Tobramycin and decreased the activity of Cemex Genta, SmartSet GMV, and VersaBond AB. The antimicrobial activity was similar for Cobalt G-HV and Palacos RG and significantly higher than that of the other cements. Furthermore, vacuum mixing also increased the number of days of elution above the breakpoint sensitivity necessary to eliminate 99% of methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA) and 85% of coagulase-negative staphylococci (CNS) recorded between 2009 and 2010. For Palacos RG, the number of days of elution increased from 2 days for manually mixed cements to 5 days for vacuum-mixed cements. For Cobalt G-HV, this value increased from 2 to 3 days; for Simplex P with Tobramycin it increased from 1 to 2 days. By contrast, vacuum mixing reduced the number of days' elution above this limit for Cemex Genta from 3 days to 1 day. The authors concluded that vacuum mixing had adverse effects on elution with low-viscosity cement (Cemex Genta), positive effects on elution with high-viscosity cements (Cobalt G-HV and Palacos RG), and unpredictable effects on elution with medium-viscosity cements (Simplex P with Tobramycin, SmartSet GMV, and VersaBond AB). Only manually mixed Cemex Genta and vacuum-mixed Palacos RG eluted antibiotics above breakpoint sensitivity on the third day; the remainder did so only on the first day. Although Cobalt G-HV and Palacos RG have a lower gentamicin load, they have greater antimicrobial activity and elution rates than other cements with a higher antibiotic load.

Other studies confirm differences between cements. Stevens et al. [40] studied the *in vitro* elution of antibiotics from Simplex and Palacos cements and noted that Palacos was a more effective vehicle for local administration [41], [42].

4.2. Choice of antibiotic

Antibiotic-loaded cement spacers release high concentrations of drug and enable higher intra-articular concentrations to be reached than parenteral antibiotics alone, with little effect on serum or urine concentrations and therefore with minimal risk of systemic damage [29], [43], [44]. It is essential to achieve local bactericidal concentrations that make it possible to eradicate infection or prevent colonization of the new implant during the reimplantation phase (the "race for the surface").

The antibiotic used must have 2 fundamental properties:

- Thermostability: Polymerization of the cement is an exothermic reaction. The cement increases in temperature within 10-13 minutes, and this change may alter the properties of the antibiotic.
- Water solubility: The antibiotic is disseminated in the tissues surrounding the infected joint. By maintaining the spacer in the joint for no less than 8 weeks, the antibiotic is released at a constant rate. However, the bactericidal effect is concentrated in the early days. Subsequently, spacers fulfill mainly a mechanical function.

The most frequently used antibiotics are tobramycin, gentamicin, vancomycin, and cephalosporins. Antibiotics can be combined to achieve broad-spectrum coverage, depending on the nature of the causative microorganism. Aminoglycoside in powder is recommended, as it does not weaken the cement; however, it is difficult to obtain in some countries. The surgeon's options are therefore limited when combining antibiotics.

Periprosthetic infections are caused mainly by gram-positive microorganisms (*S. aureus* and CNS). When the pathogen and its antibiotic sensitivity profile are clearly identified, a single antibiotic should be administered. When the pathogen is unknown, treatment is more difficult, and a combination of antibiotics can improve the chances of eradicating infection. Vancomycin covers MRSA, gentamicin covers Enterobacteriaceae and *Pseudomonas aeruginosa*, and cefotaxime destroys microorganisms resistant to gentamicin.

In addition to increasing the range of coverage, some combinations of antibiotics have a synergistic effect. Penner et al. [41] observed that the combination of vancomycin and tobramycin acted synergistically, although they discouraged the use of vancomycin in monotherapy. However, other authors have reported excellent results for CNS and MRSA with cement loaded with only 5-7.5% vancomycin (Simplex P, Howmedica, Rutherford, New Jersey, USA: 2-3 g of vancomycin per bag), both in static and in articulating spacers [45].

Synergy between aminoglycosides and vancomycin and, occasionally, a cephalosporin can make it possible to cover a broad spectrum of microorganisms. These antibiotics are usually available in powder form; however, antibiotic-loaded cements are not commercially available. Heraeus are working on a commercial presentation of gentamicin with vancomycin for commercial use in Europe in 2012.

The only commercial presentation with a synergistic effect is Copal, which combines clindamycin and gentamicin. Copal enables increased release of antibiotic and greater ability to inhibit the formation of biofilm than gentamicin alone. Ensing et al. [46] showed that the elution rate of Copal (clindamycin + gentamicin) is much greater than that of other cements, which are also considered excellent [47]. At 7 days, the elution rate was 65% for clindamycin and 41% for gentamicin; for Palacos RG the value for release was 4% for preloaded gentamicin. This increased release of antibiotic resulted in greater and more prolonged inhibition of bacterial growth on agar plates. Gentamicin-susceptible *S. aureus* strains were "small colony variants" that were resistant to gentamicin in Palacos RG and less so to the gentamicin in Copal. Elution of gentamicin in Palacos RG ceased after 72 hours, in contrast with Copal, which maintained

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bacterial inhibition during the study period. In addition, unlike Copal, Palacos RG was unable to inhibit bacterial growth of gentamicin-resistant CNS. The addition of clindamycin to gentamicin-loaded cement had an additive effect on the inhibition of biofilm. Conversely, although both cements fulfill ISO norms, the mechanical properties of Palacos RG are superior.

The study by Ensing et al. [46] has several practical implications. Synergy can enable the release of greater amounts of antibiotic, thus making inhibition of bacterial growth more effective and increasing the chances of winning the "race for the surface". By achieving high rates of antibiotic elution, even resistant bacteria can be eradicated when the dose rises sufficiently. Finally, given its worse biomechanical properties, Copal seems ideal for articulating spacers, which are withdrawn after a few weeks, but not as appropriate as Palacos RG for definitive reimplantation once the infection has been cured.

Effective elution from cement has also been observed with quinolones, daptomycin, and linezolid, although these agents are difficult to obtain in powder form or are too expensive [48]. Anguita-Alonso et al. [48] compared quinolones, cefazolin, and linezolid and found linezolid to be the most stable antibiotic after polymerization of PMMA. It achieved high peak concentrations at 7.5% and 15%. All detectable concentrations of linezolid were always above the cutoff sensitivity of *Staphylococcus* spp. (≤4 μg/mL).

Daptomycin has also demonstrated the ability to elute in local bactericidal concentrations for *S. aureus* and CNS, with a release profile similar to that of vancomycin [39], [49], [50].

4.3. Fungal infections

In the case of fungal infections, the recommended antibiotic is amphotericin B or fluconazole (Figure 4). 5-Flucytosine is not stable and is therefore not valid for use in cement. Amphotericin can cause nephrotoxicity, hepatotoxicity, chills, nausea, and blood disorders, thus necessitating lower doses and more prolonged treatment. Fortunately, the incidence of fungal infection is low. Most infections are by *Candida* species, of which *C. albicans* accounts for 60%, *C. parapsilosis* 20%, and *C. tropicalis* 20%. More uncommon species include *Coccidioides immitis*, *Sporothrix schenckii*, and *Blastomyces dermatitidis*.

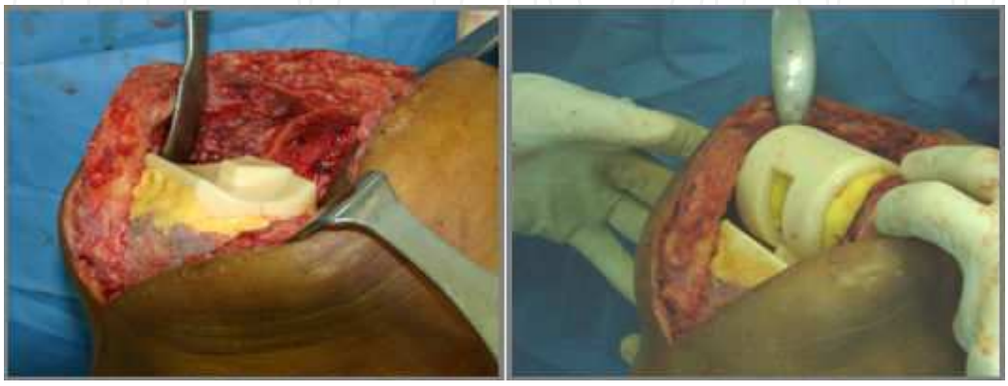

Figure 4. Preformed cement spacer with amphotericin B and fluconazole in a prosthesis with fungal infection.

Immunosuppression, prolonged hospitalization, prolonged intravenous therapy, drug dependence, and inflammatory diseases are risk factors for the development of fungal infections; however, in most published cases the patients did not present these risk factors. A reasonable postulate is that infection is caused by intraoperative inoculation rather than by hematogenous spread. The symptoms are those of a subacute infection, namely, mild to moderate pain or discomfort, effusion, and, occasionally, progressive osteolysis [51]. Published series are very short [52]-[54]. Phelan et al. [55] performed a 2-stage revision procedure with systemic administration of antifungal agents to treat 4 *Candida* infections of total joint arthroplasties. They also identified 6 other cases in the literature that had been treated with the same regimen. In addition to resection arthroplasty, 8 patients received amphotericin B alone or in combination with other antifungal agents, and 1 patient was treated with fluconazole in monotherapy. Eight patients had no recurrence of infection at a mean of 50.7 months after reimplantation.

4.4. Dose of antibiotic

Lewis [33] studied the properties of antibiotic-loaded cements. Elution typically occurs in 3 phases: an exponential phase (during the first 24 hours), a declining phase, and a final low constant elution phase. The exponential phase depends on the diffusion area of the surface of the spacer, although porosity and hydrophilicity of the cement also play a role. Porosity determines the amount of liquid that comes into contact with the surface of the cement, which in turn determines the elution rate of the antibiotic from the surface or from deeper cracks in the cement.

The addition of high doses of antibiotic to the cement is a key element of treatment when attempting to reach maximum intra-articular concentrations in the exponential phase, although some authors have observed persistent effective levels of antibiotics until 4 months after surgery [56].

The antibiotic should not exceed 20% of the total mass of cement. In addition, it should be in powder form, since liquid forms hinder polymerization. No standard ideal dosage of each drug to be mixed with bone cement has been established. Addition of 2 antibiotics to the cement is superior to the addition of 1. The most frequently used doses vary from 2.4 g of tobramycin with 1 g of vancomycin per 40 g of cement to 4 g of vancomycin with 4.6 g of tobramycin per 40 g of cement. These doses have been associated with success rates of above 90% [41], [56].

As the amount of antibiotic powder increases, the strength of the cement decreases. However, antibiotic load seems to be yet another factor within 2-stage exchange, and consistent results have been obtained using unloaded antibiotic spacers or spacers with only minimal loads. Fehring et al. [15] reported efficacious results with 1.2 g of tobramycin per 40 g of bone cement. Mean follow-up was 36 months for patients who received a nonarticulating spacer (88% eradication) and 27 months for patients treated with an articulating spacer (93% eradication).

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4.5. Resistance: Mechanical properties of cement

The factors affecting the mechanical properties of the cement are type of cement, proportion and combination of antibiotics, administration in liquid or powder form, and mixing method (manual or vacuum). Cement mixed with cloxacillin, cefazolin, gentamicin, vancomycin, and tobramycin has been shown to maintain good resistance to tension and compression [57], [58].

However, adding liquid antibiotic interferes with early polymerization, leading to a significant deterioration in the properties of the cement, because of the effect of the water and not the properties of the antibiotic itself. For example, addition of liquid gentamicin instead of powder can decrease the resistance of the cement to compression by 49% and the tensile strength by 46%. Tobramycin powder, on the other hand, had not detrimental effects on the spacers [59], [60].

Manually adding antibiotic also weakens the cement. Vacuum-mixed antibiotic-impregnated cement improves its mechanical properties by reducing porosity by up to 20%. It has been estimated that manual mixing causes a 30-40% reduction in resistance and that vacuum mixing can reduce 10-fold the rate of fracture during cyclic loading with spacers [61], [62].

Commercial antibiotic-loaded cements retain their mechanical properties, although the dose may not be sufficient for the treatment of an infection or for the manufacture of spacers, except for some commercial forms, such as Copal.

Duncan [17] reported that manual mixing decreased resistance by 36% with respect to commercially available cement, while the resistance of the latter did not differ from that of nonloaded cement.

Lewis [33] compared several cements and their biomechanical properties after combination with different antibiotics. The composition of the cement was a major factor. The elution rate of vancomycin and tobramycin from Palacos RG is superior to that of Simplex, and the elution rate of Simplex is superior to that of CMW. The combination of antibiotics is also important. Vancomycin combined with tobramycin increases elution with Palacos (the same is true of gentamicin), but with Simplex P, elution of tobramycin decreases, not vice versa. Vacuum mixing also affects elution. CMW variants decrease elution of gentamicin when vacuum-mixed; however, with Palacos the opposite occurs, as confirmed by a recent study [34]. The concentration of vancomycin did not differ significantly depending on whether the cement was mixed manually or by vacuum. These authors also studied the effect of loading and impact cycles, which can lead to minor porosity and cracks in the spacer, thus increasing the elution rate. Among the cements studied, elution only increased with Palamed G, whose porosity is higher. For the remainder, no statistically significant differences were observed between load and lack of impact on the patient.

Also important is the way in which the mixture is made. Hanssen and Spangehl [63] proposed a method for adding high doses of antibiotics to bone cement powder. Polymethylmethacrylate monomer and cement powder must first be mixed to form the liquid cement, and the antibiotic is added afterwards. It is important to leave as many large crystals as possible intact in order to create a more porous mix that increases the elution rate of the antibiotics.

This approach is not applicable when using antibiotic-loaded cement prophylactically, as crystals weaken the cement. Moreover, manual mixing decreases the elution rate in some types of cement. Therefore, commercial forms are preferred.

The method of Frommelt and Kühn [64], namely, fractional addition of antibiotic (now generally recommended), involves the gradual addition of cement and antibiotic powder and mixture of the two until the expected load of antibiotic is complete. The mixture can then be made manually or by vacuum, depending on the type of cement and the availability of vacuum systems. Once mixed, the cement has to be applied in the doughy phase or late phase of polymerization to prevent excessive interdigitation with the bone, thus facilitating extraction during surgery and providing the surgeon with a certain degree of freedom to shape the articular surface of the spacer.

4.6. Safety

As with any treatment, the surgeon must be aware of the possible side effects of the antibiotics used in spacers. Despite the large number of infected arthroplasties treated annually and the widespread use of antibiotic-loaded cement, complications are rare.

Evans [54] used 4 g of vancomycin and 4.6 g of tobramycin in powder per batch of 40 g of polymethylmethacrylate cement in 44 patients with a total of 54 periprosthetic joint infections. Follow-up to a minimum of 2 years showed no renal, vestibular, or auditory effects. Springer et al. [43] studied the systemic safety of cement loaded with high doses of antibiotic over time and reported that an average dose of 10.5 g of vancomycin and 12.5 g of gentamicin was clinically safe, with no signs of acute renal failure or other systemic side effects. In contrast, Van Raaij et al. [65] reported a case of acute renal failure that affected an 83-year-old woman after treatment with 2 g of gentamicin in a 240-g cement block combined with 7 strings of gentamicin-loaded polymethylmethacrylate beads. Serum levels of gentamicin were high, leading to removal of the spacer and eventual recovery of renal function. Ceffa et al. [66] reported 2 cases of mucormycosis after treatment with antibiotic-loaded cement spacers.

The complications reported are rare events in which other factors (eg, blood volume or intravenous antibiotics) could play a role, since the normalization profile of serum antibiotic levels, when using antibiotic-loaded spacers, is exponential and reaches normal values in 24 hours.

5. Results

The use of a polymethylmethacrylate antibiotic-loaded spacer provides not only more effective treatment of periprosthetic infection, with eradication rates ranging from 90% to 100% in the literature, but also improved function, reduced pain, greater patient satisfaction, shorter hospital stay, and lower costs. Few studies analyze developments in the medium-to-long term. Although the results remain more or less stable, up to 30% of patients require revision for loosening, reinfection, or other causes in the medium term [67].

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Several studies compare the results of 2-stage exchange with articulating spacers and 28 studies compare the results with a static spacer [3].

Park et al. [68] compared 20 prosthetic knee infections treated with monoblock spacers and 16 treated with articulating spacers. The reinfection rate was 6.3% for the articulating group and 15% for the fixed group. The range of motion with the spacer was 80º and 9º, respectively (final range, 108º and 92º). The clinical and functional score according to the HSS scale was significantly better with the articulating spacer, and the number of extensile exposures was lower. In the static spacer group, 75% of patients (65% of the femurs and 50% of the tibias) had bone loss. This complication was not observed for the articulating spacers.

Meek et al. [27] retrospectively analyzed the results of 2-stage exchange with a PROSTALAC articulating spacer in 47 patients with infected knee prosthesis and a mean follow-up of 41 months. The eradication rate was 96%. The Western Ontario and McMaster Universities Osteoarthritis scale and the Oxford-12 and Short Form-12 scales showed better scores for articulating spacers.

Calton et al. [9] compared the outcomes of patients treated with articulating spacers and patients treated with nonarticulating spacers. Among the 24 patients with a nonarticulating spacer, 60% had an average bone loss of 6.2 mm in the tibia and 12.8 mm in the femur, often with invagination and migration of the spacer and problems of soft tissue retraction. The authors recommended intramedullary extension of the spacer to prevent migration and obtain the appropriate thickness. They also recommended tightening the collateral ligaments to prevent contracture and a block that is sufficiently wide to rest on the cortical rim and prevent migration to cancellous bone. No differences were observed between the groups in eradication rates, time of surgery, or functional outcome.

Fehring et al. [15] studied 25 nonarticulating spacers and 30 articulating spacers and found that articulating spacers facilitated reimplantation and were not associated with bone loss.

Emerson et al. [13] reported that range of motion was greater with articulating knee spacers than with nonarticulating spacers; flexion of the knee averaged 107.8° and 93.7°, respectively, and no evidence of higher complication rates was found.

Therefore, a comprehensive review of the literature provides more arguments for articulating spacers than for static spacers. Articulating spacers seem to be the most widespread form of treatment. The method of making the spacer does not seem to affect eradication rates or functional outcome.

Durbhakula et al. [21] treated 4 patients with antibiotic-loaded articulating spacers made in vacuum-injected silicone molds designed to produce articulating femoral and tibial components. The final average range of motion was 104° and the HSS score was 82. The rate of eradication of infection was 92% after an average of 33 months. A system of this type does not require a metal-polyethylene articulation surface and reduces costs by applying reusable molds that cost about $300 each. The authors reported no problems of dislocation, retraction, bone loss, fracture, or fragmentation of the spacer.

Goldstein et al. [23] formed spacers intraoperatively using cement and test components on aluminum foil to prevent interdigitation. The femoral condyles were molded with the tibial trial implant, and the tibial implant was used to calculate the size and thickness of the cemented tibial component. The authors reported initial success in 5 patients.

MacAvoy and Ries [20] described an inexpensive mold-based method for manufacturing a spherical articulating spacer (ball and socket). They used this method in cases with severe bone deficiency and damage to the ligaments because of its high congruence. The average load was 3.6 g to 4 g of tobramycin + 1 g of vancomycin per bag of Palacos. For an average of 4 cements, this represents a dose of more than 14 g. In 12 patients with severe comorbidities, infection was eradicated in 9 of 13 knees with a mean follow-up of 28 months. All patients could walk with minimal assistance. The average range of motion of the knee with the spacer was 79°, which increased to 98° at the end of treatment. The authors rarely used hinge models, despite serious injury to the ligaments and bone loss.

Using cement spacer molds created intraoperatively with Palacos RG loaded with 0.5 g of gentamicin plus 3 g of vancomycin, Shen et al. [25] obtained 10 reimplantations in 17 cases followed for 30 months. In 5 cases, the spacer was the definitive treatment, in 1 case the joint merged, and 1 patient required amputation. The average range of motion with the spacer was 82° (97° after reimplantation).

Excellent results have been reported with the Hoffman prosthesis-spacer system. Anderson et al. [30] reported a range of motion of 2° to 115°; Huang et al. [69] reported 97.6°, which was smaller than in previous publications (104º to 115º). As for eradication with this type of spacer, reinfection rates are variable: 4% according to Anderson et al. [30] (25 knees), 0%-12% according to Hofmann et al. [29] (22 and 50 patients; Simplex cement with 4.8 g of vancomycin per bag), 9% according to Emerson et al. [13] (22 patients), and 2% according to Cuckler [70] (44 patients).

Ha [24] reported motion ranging from 2° to 104° with manually modeled cement spacers. The study included 12 cases treated with spacers made using the double mold (a cement negative is made with trial components and the definitive spacer is modeled on the negative) and using doses of 4.8 g of tobramycin and 4 g of vancomycin per cement bag. The antibiotic load accounted for 20% of the cement-antibiotic composite.

In addition to the type of spacer, range of motion is influenced by preoperative mobility, the state of the soft tissues, surgical technique, implant selection, early rehabilitation, and patient cooperation. Our group [18] found the range of motion to be 107° after reimplantation using manual spacers and 7.5% antibiotic load.

Soft tissue damage, severe bone loss or general health status, appear to be more important than the treatment method, and the results of 2-stage exchange, which are generally excellent, are much worse in patients with a less favorable health status.

Macmull et al. [71] published 19 cases with the SMILES spacer, which was based on an antibiotic-loaded hinge coated with antibiotic-loaded cement (Palacos RG, Heraeus Medical GmbH, Wehrheim, Germany). The spacer was used in the early stages of chronic infection

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associated with severe bone loss on revision arthroplasty in 11 cases (58%), tumor endoprostheses in 4 (21%), primary arthroplasty in 2 (11%), and infection on fracture or osteotomy in 2. The eradication rate at 38 months was 63% (12 cases), Four patients (21%) suffered reinfection and 2 were amputees. Jeys et al. [72] reported an eradication rate of 72% in primary infection of massive tumor prosthesis with a 2-stage protocol.

Reinfection after reimplantation has not been adequately studied in the literature, although the high percentage of rescue treatments indicates that reinfection has its own prognostic implications. Therefore, it could be classified as a separate type of infection and independently studied in the future.

Hanssen et al. [73] published a series of 24 reinfections after infected total knee prosthesis. The infection was eradicated in only 1 case. Another patient received suppressive therapy after a new reimplantation, and the rest underwent arthrodesis.

Hart and Jones [74] reported 6 cases of reinfection following 2-stage revision. The infection was eradicated in 2 cases (with another 2-stage revision), 2 patients had bone fusions, and 2 had suppressive treatments.

6. Conclusions

1. Two-stage exchange is considered the treatment of choice in the following circumstances: late infection, unidentified causal microorganisms, fungal infections, infections by virulent organisms, underlying inflammatory diseases, immunosuppression, and reinfection after reimplantation.
2. Articulating spacers can minimize complications between procedures, thus enhancing patient autonomy and mobility, preventing retraction of the soft tissues, and facilitating reimplantation.
3. In addition, articulating spacers seem to improve eradication rates and functional outcomes and reduce complications.
4. The way the spacer is constructed does not seem to affect eradication rates and functional outcome. The surgeon's choice of spacer will depend on technical and financial restraints. Despite their advantages and disadvantages, all types of spacer have demonstrated consistent and reproducible results.
5. Not all cements are equally suitable for the prevention and treatment of infection.
6. The antibiotic should be added as powder to avoid weakening the cement. Appropriate use of synergies increases the spectrum of coverage and elution rate of certain antibiotics.
7. Once fractionated addition is complete, vacuum mixing increases the elution of the antibiotic from the spacer when high-viscosity cements are used. Manual mixing is preferred when low-viscosity cements are used.

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References

[1] Sharkey, P. F, Hozack, W. J, Rothman, R. H, Shastri, S, & Jacoby, S. M. Why Are Total Knee Arthroplasties Failing Today?. Clin Orthop (2002). , 404, 7-13.

[2] Iorio, R, Healy, W. L, & Richards, J. A. Comparison of the hospital cost of primary and revision total knee arthroplasty after cost containment. Orthopedics (1999). , 22, 195-199.

[3] Jämsen, E, Stogiannidis, I, Malmivaara, A, Pajamäki, J, Puolakka, T, & Konttinen, Y. T. Outcome of prosthesis exchange for infected knee arthroplasty: the effect of treatment approach. A systematic review of the literature. Acta Orthopaedica (2009). , 80, 67-77.

[4] Windsor, R. E, Insall, J. N, Urs, W. K, Miller, D. V, & Brause, B. D. Two-stage reimplantation for the salvage of total knee arthroplasty complicated by infection: further follow-up and refinement of indications. J Bone Joint Surg Am (1990). A.: 272-8., 72.

[5] Borden, L. S. Gearen PF: Infected total knee arthroplasty: A protocol for management. J Arthroplasty (1987). , 2, 27-36.

[6] Wilde, A. H, & Ruth, J. T. Two stage reimplantation in infected total knee arthroplasty. Clin Orthop (1988). , 23-35.

[7] Booth, R. E, & Lotke, P. A. The results of spacer block technique in revision of infected total knee arthroplasty. Clin Orthop (1989).

[8] Hoffman, A. A, Kane, K. R, Tkach, T. K, Plaster, R. L, & Camargo, M. P. Treatment of infected total knee replacement arthroplasty using an articulating spacer. Clin Orthop (1995). , 321, 44-54.

[9] Calton, T. F, Fehring, T. K, & Griffin, W. L. Bone loss associated with the use of spacer blocks in infected total knee arthroplasty. Clin Orthop (1997). , 345, 148-54.

[10] Jiranek, W. A, Arlen, D, Hanssen, A. D, & Greenwald, A. S. Antibiotic-loaded bone cement for infection prophylaxis in total joint replacement. J Bone Joint Surg Am. (2006). , 88, 2487-2500.

[11] Alt, V, Bechert, T, & Steinrücke, P. In vitro testing of antimicrobial activity of bone cement. Antimicrob Agents Chemother (2004). , 48, 4084-8.

[12] Cohen, J. C, Hozack, W. J, Cucker, J. M, & Booth, R. E. Two stage reimplantation of septic total knee arthroplasty: report of three cases using an antibiotic PMMA spacer block. J Arthroplasty (1988). , 3, 369-77.

[13] Emerson Jr RHMuncie M, Tarbox TR, Higgins LL. Comparison of a static with a mobile spacer in total knee infection. Clin Orthop (2002). , 404, 132-8.

[14] Cui, Q, Mihalko, W. M, Shields, J. S, Ries, M, & Saleh, K. J. Antibiotic-impregnated cement spacers for the treatment of infection associated with total hip or knee arthroplasty. J Bone Joint Surg Am (2007). , 89, 871-82.

[15] Fehring, T. K, Odum, S, Calton, T. F, & Mason, J. B. Articulating versus static spacers in revision total knee arthroplasty for sepsis. The Ranawat Award. Clin Orthop (2000). , 380, 9-16.

[16] Chiang, E. R, Su, Y. P, Chen, T. H, Chiu, F. Y, & Chen, W. M. Comparison of articulating and static spacers regarding infection with resistant organisms in total knee arthroplasty. Acta Orthopaedica (2011). , 82, 460-464.

[17] Duncan, C. P, Beauchamp, C. P, & Masri, B. The antibiotic loaded joint replacement system: A novel approach to the management of the infected knee replacement. J Bone Joint Surg Br (1992). suppl III): 296

[18] Villanueva-martínez, M, Ríos-luna, A, Pereiro, J, & Fahandez-saddi, H. Hand-made articulating spacers in two-stage revision for infected total knee arthroplasty: good outcome in 30 patients. Acta Orthop Scand (2008). , 79, 674-82.

[19] Mcpherson, E. J, Lewonowski, K, & Dorr, L. D. Techniques in arthroplasty. Use of an articulated PMMA spacer in the infected total knee arthroplasty. J Arthroplasty (1995). , 10, 87-89.

[20] MacAvoy MCRies MD. The ball and socket articulating spacer for infected total knee arthroplasty. J Arthroplasty (2005). , 20, 757-62.

[21] Durbhakula, S. M, Czajka, J, Fuchs, M. D, & Uhl, R. L. Antibiotic-loaded articulating cement spacer in the 2-stage exchange of infected total knee arthroplasty. J Arthroplasty (2004). , 19, 768-74.

[22] Hsu, Y. C, Cheng, H. C, & Ng, T. P. Antibiotic-loaded cement articulating spacer for 2-stage reimplantation in infected total knee arthroplasty: a simple and economic method. J Arthroplasty (2007). , 22, 1060-6.

[23] Goldstein, W. M, Kopplin, M, Wall, R, & Berland, K. Temporary articulating methyl-methacrylate antibiotic spacer (TAMMAS): a new method of intraoperative manufacturing of a custom articulating spacer. J Bone Joint Surg. (2001). S, 2, 92-97.

[24] Ha, C. W. A technique for intraoperative construction of antibiotic spacers. Clin Orthop (2006). , 445, 204-9.

[25] Shen, H, Zhang, X, Jiang, Y, Wang, Q, & Chen, Y. Qi Wang Q, Shao J. Intraoperatively-made cement-on-cement antibiotic-loaded articulating spacer for infected total knee arthroplasty. The Knee (2010). , 17(2010), 407-411.

[26] Pitto, R. P, Castelli, C. C, Ferrari, R, & Munro, J. Pre-formed articulating knee spacer in two-stage revision for the infected total knee arthroplasty. Int Orthop (2005). , 29, 305-8.

[27] Meek, R. M, Masri, B. A, Dunlop, D, Garbuz, D. S, Greidanus, N. V, Mcgraw, R, & Duncan, C. P. Patient satisfaction and functional status after treatment of infection at the site of a total knee arthroplasty with use of the PROSTALAC articulating spacer. J Bone Joint Surg Am (2003). , 85, 1888-92.

[28] Haddad, F. S, Masri, B. A, Campbell, D, Mcgraw, R. W, Beauchamp, C. P, & Duncan, C. P. The PROSTALAC functional spacer in two-stage revision for infected knee replacements: prosthesis of antibiotic-loaded acrylic cement. J Bone Joint Surg Br (2000). , 82, 807-12.

[29] Hofmann, A. A, Goldberg, T, Tanner, A, & Kurtin, S. M. Treatment of infected total knee arthroplasty using an articulating spacer: 2- to 12-year experience. Clin Orthop (2005). , 430, 125-31.

[30] Anderson, J. A, Sculco, P. K, Heitkemper, S, Mayman, D. J, Bostrom, M. P, & Sculco, T. P. An articulating spacer to treat and mobilize patients with infected total knee arthroplasty. J Arthroplasty (2009). , 24, 631-5.

[31] Incavo, S. J, Russell, R. D, Mathis, K. B, & Adams, H. Initial Results of Managing Severe Bone Loss in Infected Total Joint Arthroplasty Using Customized Articulating Spacers. J Arthroplasty. (2009). , 24, 607-13.

[32] Macmull, S, Bartlett, M. J, Blunn, G. W, Pollock, R. C, Carrington, R. W, Skinner, J. A, Cannon, S. R, & Briggs, T. W. Custom-made hinged spacers in revision knee surgery for patients with infection, bone loss and instability. The Knee (2010). , 17, 403-406.

[33] Lewis, G. Review Properties of Antibiotic-Loaded Acrylic Bone Cements for Use in Cemented Arthroplasties: A State-of-the-Art Review. J Biomed Mater Res Part B: Appl Biomater (2009). B: , 558-574.

[34] Meyer, J, Piller, G, Spiegel, C. A, Hetzel, S, & Squire, M. Vacuum-Mixing Significantly Changes Antibiotic Elution Characteristics of Commercially Available Antibiotic-Impregnated Bone Cements. J Bone Joint Surg Am (2011). , 93, 2049-56.

[35] Dunne, N, Hill, J, Mcafee, P, Todd, K, Kirkpatrick, R, Tunney, M, & Patrick, S. In vitro study of the efficacy of acrylic bone cement loaded with supplementary amounts of gentamicin. Effect on mechanical properties, antibiotic release, and biofilm formation. Acta Orthopaedica (2007). , 78(6), 774-785.

[36] Nelson, C. L, Griffin, F. M, Harrison, B. H, & Cooper, R. E. In vitro elution characteristics of commercially and noncommercially prepared antibiotic PMMA beads. Clin Orthop Relat Res. (1992). , 284, 303-9.

[37] Kuehn, K. D, Ege, W, & Gopp, U. Acrylic bone cements: composition and properties. Orthop Clin North Am. (2005). , 36, 17-28.

[38] Greene, N, Holtom, P. D, Warren, C. A, Ressler, R. L, Shepherd, L, Mcpherson, E. J, & Patzakis, M. J. In vitro elution of tobramycin and vancomycin polymethylmethacrylate beads and spacers from Simplex and Palacos. Am J Orthop (1998). , 27, 201-205.

[39] Kuechle, D. K, Landon, G. C, Musher, D. M, & Noble, P. C. Elution of vancomycin, daptomycin, and amikacin from acrylic bone cement. Clin Orthop Relat Res (1991). , 264, 302-8.

[40] Stevens, C. M, Tetsworth, K. D, Calhoun, J. H, & Mader, J. T. An articulated antibiotic spacer used for infected total knee arthroplasty: a comparative in vitro elution study of Simplex and Palacos bone cements. Journal of Orthopaedic Researh (2005). , 23, 27-33.

[41] Penner, M. J, Masri, B. A, & Duncan, C. P. Elution characteristics of vancomycin and tobramycin combined in acrylic bone-cement. J Arthroplasty. (1996). , 11, 939-44.

[42] Greene, N, Holtom, P. D, Warren, C. A, Ressler, R. L, Shepherd, L, Mcpherson, E. J, & Patzakis, M. J. In vitro elution of tobramycin and vancomycin polymethylmethacrylate beads and spacers from Simplex and Palacos. Am J Orthop. (1998). , 27, 201-5.

[43] Springer, B. D, Lee, G. C, Osmon, D, Haidukewych, G. J, Hanssen, A. D, & Jacofsky, D. J. Systemic safety of high-dose antibiotic-loaded cement spacers after resection of an infected total knee arthroplasty. Clin Orthop Relat Res (2004). , 427, 47-51.

[44] Hanssen, A. D, & Spangehl, M. J. Practical applications of antibiotic-loaded bone cement for treatment of infected joint replacements. Clin Orthop Relat Res (2004). , 427, 79-85.

[45] Chiang, E. R, Su, Y. P, Chen, T. H, Chiu, F. Y, & Chen, W. M. Comparison of articulating and static spacers regarding infection with resistant organisms in total knee arthroplasty. Acta Orthopaedica (2011). , 82(4), 460-464.

[46] Ensing, G. T, Van Horn, J. R, Van Der Mei, H. C, Busscher, H. J, & Neut, D. Copal Bone Cement Is More Effective in Preventing Biofilm Formation than Palacos R-G. Clin Orthop Relat Res (2008). , 466, 1492-1498.

[47] Neut, D, De Groot, E. P, Kowalski, R. S, Van Horn, J. R, Van Der Mei, H. C, & Busscher, H. J. Gentamicin-loaded bone cement with clindamycin or fusidic acid added: biofilm formation and antibiotic release. J Biomed Mater Res (2005). , 165-170.

[48] Anguita-alonso, P, Rouse, M. S, Piper, K. E, Jacofsky, D. J, Osmon, D. R, & Patel, R. Comparative study of antimicrobial release kinetics from polymethylmethacrylate. Clin Orthop Relat Res (2006). , 445, 239-244.

[49] Webb, N. D, Mccanless, J. D, Courtney, H. S, Bumgardner, J. D, & Haggard, W. O. Daptomycin Eluted From Calcium Sulfate Appears Effective Against Staphylococcus. Clin Orthop Relat Res. (2008). , 466(6), 1383-1387.

[50] Hall, E. W, Rouse, M. S, Jacofsky, D. J, Osmon, D. R, Hanssen, A. D, Steckelberg, J. M, & Patel, R. Release of daptomycin from polymethylmethacrylate beads in a continuous flow chamber. Diagnostic Microbiology and Infectious Disease (2004). , 50, 261-265.

[51] Wyman, J, Mcgough, R, & Limbird, R. Fungal infection of a total knee prosthesis: Successful treatment using articulating cement spacers and staged reimplantation. Orthopedics (2002). , 25, 1391-4.

[52] Baumann, P. A, Cunningham, B, Patel, N. S, & Finn, H. A. Aspergillus fumigatus infection in a mega prosthetic total knee arthroplasty: salvage by staged reimplantation with 5-year follow-up. J Arthroplasty (2001). , 16, 498-503.

[53] Langer, P, Kassim, R. A, Macari, G. S, & Saleh, K. J. Aspergillus infection after total knee arthroplasty. Am J Orthop (2003). , 32, 402-4.

[54] Evans, R. P. Successful treatment of TH and TK infection with articulating antibiotic components. A modified treatment method. Clin Orthop Relat Research. (2004). , 427, 37-46.

[55] Phelan, D. M, Osmon, D. R, Keating, M. R, & Hanssen, A. D. Delayed reimplantation arthroplasty for candidal prosthetic joint infection: a report of 4 cases and review of the literature. Clin Infect Dis (2002). , 34, 930-8.

[56] Masri, B. A, Duncan, C. P, & Beauchamp, C. P. Long-term elution of antibiotics from bone-cement: an in vivo study using the prosthesis of antibiotic-loaded acrylic cement (PROSTALAC) system. J Arthroplasty (1998). , 13, 331-8.

[57] Armstrong, M. S, Spencer, R. F, Cunningham, J. L, Gheduzzi, S, Miles, A. W, & Learmonth, I. D. Mechanical characteristics of antibiotic-laden bone cement. Acta Orthop Scand (2002). , 73, 688-90.

[58] Klekamp, J, Dawson, J. M, Haas, D. W, Deboer, D, & Christie, M. The use of vancomycin and tobramycin in acrylic bone cement: biomechanical effects and elution kinetics for use in joint arthroplasty. J Arthroplasty (1999). , 14, 339-46.

[59] Seldes, R. M, Winiarsky, R, Jordan, L. C, Baldini, T, Brause, B, Zodda, F, & Sculco, T. P. Liquid gentamicin in bone cement: a laboratory study of a potentially more cost-effective cement spacer. J Bone Joint Surg Am (2005). , 87, 268-72.

[60] Deluise, M, & Scott, C. P. Addition of hand-blended generic tobramycin in bone cement: effect on mechanical strength. Orthopedics (2004). , 27, 1289-91.

[61] Kuehn, K. D, Ege, W, & Gopp, U. Acrylic bone cements: mechanical and physical properties. Orthop Clin North Am (2005). , 36, 29-39.

[62] Kuehn, K. D, Ege, W, & Gopp, U. Acrylic bone cements: composition and properties. Orthop Clin North Am (2005). , 36, 17-28.

[63] Hanssen, A. D, & Spangehl, M. J. Treatment of the infected hip replacement. Clin Orthop Relat Res (2004). , 420, 63-71.

[64] Frommelt, L, & Kühn, K. D. Antibiotic-loaded cement. In: Breusch SJ, Malchau M. The well-cemented total hip arthroplasty. Heidelberg: Springer, (2005). , 86-92.

[65] Van Raaij, T. M, Visser, L. E, Vulto, A. G, & Verhaar, J. A. Acute renal failure after local gentamicin treatment in an infected total knee arthroplasty. J Arthroplasty (2002). , 17, 948-50.

[66] Ceffa, R, Andreoni, S, Borre, S, Ghisellini, F, Fornara, P, Brugo, G, & Ritter, M. A. Mucoraceae infections of antibiotic-loaded cement spacers in the treatment of bacterial infections caused by knee arthroplasty. J Arthroplasty (2002). , 17, 235-8.

[67] Haleem, A. A, Berry, D. J, & Hanssen, A. D. Mid-Term to Long-Term Followup of Two-stage Reimplantation for Infected Total Knee Arthroplasty. Clin Orthop Relat Research (2004). , 428, 35-39.

[68] Park, S. J, Song, E. K, Seon, J. K, Yoon, T. R, & Park, Y. H. Comparison of static and mobile antibiotic-impregnated cement spacers for the treatment of infected total knee arthroplasty. International Orthopaedics (SICOT) (2010). , 34, 1181-1186.

[69] Huang, H, Su, J, & Chen, S. The results of articulating spacer technique for infected total knee arthroplasty. J Arthroplasty (2006). , 21, 1163-8.

[70] Cuckler, J. M. The infected total knee. Management options. J Arthroplasty (2005). S , 2, 33-6.

[71] Macmull, S, Bartlett, W, Miles, W, Blunn, J, Pollock, G. W, Carrington, R. C, Skinner, R. W, Cannon, J. A, Briggs, S. R, & Custom-made, T. W. hinged spacers in revision knee surgery for patients with infection, bone loss and instability. The Knee (2010). , 17, 403-406.

[72] Jeys, J L. M, Grimer, S. R, & Tillman, R. M. Periprosthetic infection in patients treated for an orthopaedic oncological condition. Bone Jt Surg Am (2005). , 87, 842-9.

[73] Hanssen, A. D, Trousdale, R. T, & Osmon, D. R. Patient outcome with reinfection following reimplantation for the infected total knee arthroplasty. Clin Orth Relat Res (1995). , 321, 55-67.

[74] Hart, W. J, & Jones, R. S. Two-stage revision of infected total knee replacements using articular cement spacers and short-term antibiotic therapy. J Bone J Surg Br (2006). , 88, 1011-5.