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Two-stage reimplantation in periprosthetic knee infection

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Abstract. – OBJECTIVE: The increasing number of total knee arthroplasties performed yearly worldwide has resulted in a concomitant rise in bacterial infections. Two-stage reimplantation has been reported as the most successful method of treating periprosthetic knee infections. The purpose of this study was to describe all the phases of the two-stage reimplantation and to review the literature regarding the topic.

MATERIALS AND METHODS: Most significant and recent papers about the management of periprosthetic knee infection through a two-stage reimplantation protocol were carefully analysed and reviewed. Our personal experience, previously published, with two-stage-reimplantation protocol was also briefly reported.

RESULTS: Two-stage reimplantation has been reported as the most successful method of treating periprosthetic knee infections. The strategy of using an antibiotic-loaded cement spacer and intravenous antibiotics with delayed exchange arthroplasty is actually considered the state-of-the-art, with a reported success rate of 88-96%. The two-stage protocol has been reported as a viable option also for patients with a periprosthetic knee infection by multidrug-resistant organisms. On the other hand, open debridement with polyethylene exchange and single-stage reimplantation have been reported effective only in selective case series involving acute infections by low-virulence organisms.

CONCLUSIONS: The strategy that involves the use of cement spacer, intravenous antibiotic therapy, and successive revision total knee implantation is nowadays considered the gold standard for the management of the periprosthetic knee infection. This treatment is actually considered the first choice not only for chronic but also for acute infections, especially in the presence of resistant bacteria.

Key Words

Two-stage reimplantation, Knee infection, Revision, Cement spacer.

Introduction

The improvement in outcomes and modern prosthesis design ensured that total knee arthroplasty (TKA) is now a commonly performed surgery. However, the increasing number of total knee replacements performed yearly worldwide resulted also in a rise in periprosthetic infections. It was postulated that a total of 2-5% of the primary and revision TKA becomes infected every year, requiring a revision procedure, actually based on two-stage procedure[1,2].

The diagnosis and treatment of these periprosthetic infections is a major and challenging issue, requiring precise identification of the pathogen, meticulous debridement, and postoperative rehabilitation. Despite the use of systemic antibiotic prophylaxis, strict hygienic protocols and special sterile enclosure with laminar flow, the infection rate in primary TKA remains between 0.5 and 3%, and infection represents the second cause of TKA failure in absolute[3-10] (Figure 1). Furthermore, during the last 15 years, an increasing number of TKAs infected by multidrug-resistant bacteria has been reported[7,11,12,64]. In case of a periprosthetic joint infection related to multidrug-resistant bacteria, the failure rate is high, with possible final implant loosening[11,65].

The diagnosis of periprosthetic joint infection (PJI) is challenging. To help the physician in the early identification of PJI the Infectious Diseases Society of America (IDSA) and both the Musculoskeletal Infection Society (MIS) and European Bone and Joint Infection Society (EBJIS), during the 2013 International Consensus Conference, proposed some diagnostic criteria (Tables I and II)[62,63].

The optimal management of an infected TKA should both eradicate the infection and restore a painless and well-functioning joint. The treatment of an infected TKA is still controversial,

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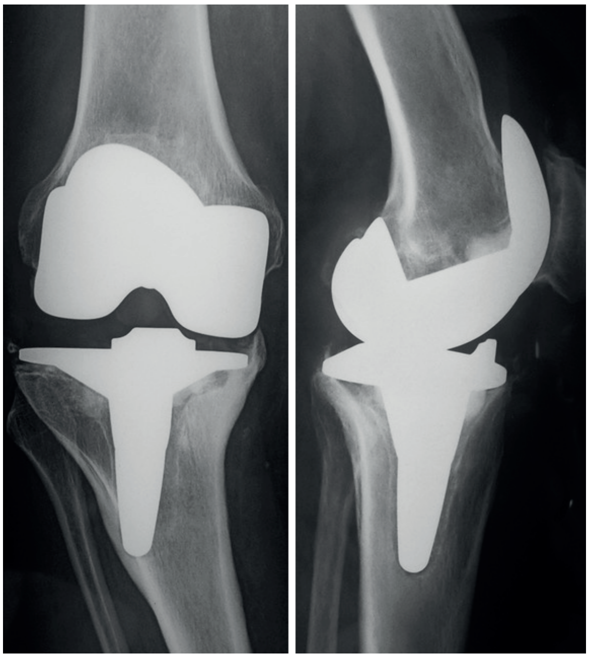

Figure 1. Infection still represents the second most common cause of implant failure after aseptic loosening in TKA.

and different surgical options are available: open debridement with polyethylene exchange, single- and two-stage reimplantation[13-16]. However, open debridement with polyethylene exchange and single-stage reimplantation have been reported effective only in selective case-series (especially involving acute infections), and in the presence of low-grade periprosthetic infections[17]. On the other hand, two-stage reimplantation has been reported as the most successful method of treating TKA infections, both acute and chronic[2,18,19,20]. During the first stage, all prosthetic components and cement are removed, and an antibiotic-loaded cement spacer is positioned into the joint. After 6-12 weeks of concomitant specific antibiotic therapy, the spacer is removed and a revision TKA is implanted. The strategy of using antibiotic-loaded cement spacers and intravenous (with or without oral) antibiotics with delayed exchange arthroplasty is actually considered the state-of-the-art with a reported success rate of 88-96% in infection eradication and function preservation[2,5,19-27].

The purpose of this study was to describe all the phases of the two-stage reimplantation and to review the literature regarding the topic. Our personal experience, previously published, with two-stage-reimplantation protocol was briefly reported.

Table I. Musculoskeletal Infection Society Criteria.

Musculoskeletal Infection Society and European Bone and Joint Infection Society
Definite PJI: Sinus tract communicating with joint OR growth of same organism in 2 or more periprosthetic tissue cultures
Possible PJI: three or more of the following minor criteria: • Erythrocyte sedimentation rate (ESR) >30 mm/hr AND C-reactive protein (CRP) >10 mg/l • Synovial fluid white blood count >3,000 cells/µl or ++ change on leukocyte-esterase test strip • Synovial fluid PMN >80% • >5 PMN/HPF on histologic analysis of periprosthetic frozen section • A single positive culture

PMN, polymorphonuclear neutrophils; **HPF**, high-power field (microscopy)

Implant removal and use of cement spacer

The first stage involves irrigation and debridement of all necrotic and infected tissue, complete synovectomy, and removal of all prosthetic components and cement. Multiple specimens are obtained from the bone cement interface and soft tissues. These specimens are used for aerobic, anaerobic and fungal cultures, and for permanent histological analysis. To improve the microbiological culture diagnosis accuracy, sonication of the removed implant is available, and useful especially in patients who under antibiotics. The sensitivity of sonication in detecting bacterial growth has been reported higher than conventional culture[28]. Afterwards, the resected bone and joint space are thoroughly irrigated, and an impregnated-antibiotic cement spacer is positioned into joint (Figure 2). There are many

Table II. Infectious Diseases Society of America Criteria.

Infectious Diseases Society of America
Definite PJI: sinus tract communicating with joint OR growth of same organism in 2 or more periprosthetic tissue cultures OR the presence of purulence surrounding the prosthesis without an alternative cause
Possible PJI: any of the following: • Growth of a virulent organism from a single tissue biopsy or synovial-fluid sample • Presence of acute inflammation on histopathologic examination of periprosthetic tissue at time of surgical debridement of prosthesis removal

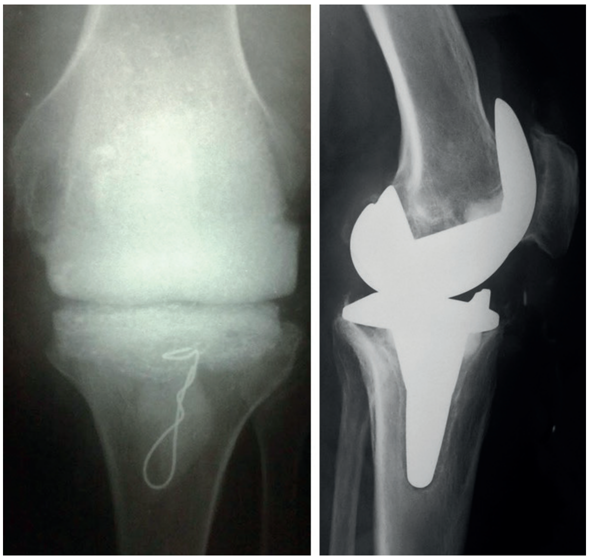

Figure 2. Antibiotic-loaded cement spacer aims to preserve joint space and avoid collateral ligaments retraction during the stages. Additionally, spacer allows the delivery of high-dose local antibiotics to the knee greater than intravenous administration.

advantages using cement spacers: space preservation; reduction of the scar tissue that could compromise soft-tissue elasticity (especially for the collateral ligaments) and thus their balancing during reimplantation; improvement of patient's comfort between the stages; delivery of high-dose local antibiotics to the knee greater than intravenous administration[15]. Three types of cement spacers have been proposed for the treatment of infected TKAs: block spacers and two types of articulated spacers. These latter are distinguished in two types. The first one is made completely of antibiotic-impregnated cement, with or without preformed molds. The second one is made of metal and plastic components, coated with antibiotic-impregnated cement (composite spacer).

During the 2013 International Consensus Conference delegates supported the use of articulated over non-articulated spacers in terms of functional outcomes[63].

Block Spacers

Static or block spacers have the advantages of being cost-effective and simple to use; additionally, block spacers minimize debris generation while treating the infection[29]. Anyway, some concerns exist about the use of block spacers. In fact, block spacers do not allow knee flexion before reimplantation, resulting in possible quadriceps scarring and arthrofibrosis[30,31]. Significant femoral and tibial bone loss could occur with migration or invagination of an undersized block spacer into weakened cancellous bone[32]. Mobilization of the spacer can cause frictional bone erosion[33]. Disuse of the extremity before reimplantation could cause osteopenia[24,34] with consequent bone loss and further knee stiffness[35]. Wound healing problems[36,37] and compression of neurovascular structures[38], due to the block spacer mobilization, have been reported, too. Stiffness and arthrofibrosis from block spacer could make necessary a more aggressive surgical exposure at the second stage reimplantation, with the need of approaches such as quadriceps snip, other quadriceps plasties or tibial tubercle osteotomy, that could compromise extensor mechanism and collateral ligaments integrity of the re-implanted knee arthroplasty[29,39].

Articulated Spacers

Introduction of articulated spacers has greatly increased the comfort for the patients before reimplantation. Moreover, accurate manufacturing or hand-molding of these spacers reduced, if not cancelled, the risk of catastrophic failure and complications[40,41]. Articulated spacers present many advantages when compared to static spacers. Articulated spacers allow both weight-bearing and knee motion during the period of antibiotic therapy, avoiding stiffness and osteopenia by disuse[15,35,42,43]. Femoral and tibial components of the articulated spacers, both preformed or molded directly in the surgery room, can be better adapted to the different sizes of the residual bone, avoiding early mobilization and consequent bone friction and erosion[29,35]. The ability to flex the knee between the stages improves patient satisfaction and final knee function without compromising the infection eradication rate[29,42,44]. At reimplantation stage, removal of articulated spacers is less invasive and does not require special instrumentation. The reimplantation procedure is facilitated by decreased quadriceps scarring, maintenance of collateral ligament integrity and preserved bone stock, with optimal functional outcomes[24,43,45] and implant survivorship[15,29,35,44,46].

A recent metanalysis[20] demonstrated that articulating spacers could provide significantly better range of motion (ROM) and knee function scores after revision surgery compared to the static spacer, without affecting infection eradication rate, soft tissue contracture during exclusion period, and knee pain scores.

Anyway, articulated spacers might be unappropriated in infected TKA with extensor mechanism disruption, severe ligamentous instability or bone loss. In fact, in these cases, they present a high risk of severe complications, like spacer dislocation and wound dehiscence or neurovascular injuries. It may be necessary to add cement stems to the spacer to achieve greater stability of the knee between the stages, avoiding thus serious complications[47].

Choice of antibiotics

Most of the preformed articulated spacers contain gentamicin, whereas articulated spacers e molded in surgery room can be loaded using those antibiotics specific for the infecting organisms. Anyway, the antibiotic of choice must be not deactivated by the cement polymerization process.

The cement used to make a block spacer or to fix an articulated spacer to the bone is generally added by 2 g of vancomycin and 2.4 g of tobramycin each 40 g pack of cement[39,48]. The antibiotics contained in the cement are released into surrounding tissues by a diffusion process that primarily depends on the type of cement used, surface area and volume of cement, and the dose of antibiotics used[49].

Cuckler and Hofmann separately used tobramycin 4.8 g for 40 g of bone cement for their series[24,34]. Durbhakula et al[47] preferred a ratio of 2.4 g of tobramycin and 1 g of vancomycin each pack of bone cement. Nazarian et al[26] made a block spacer consisting of 80 g of Palacos acrylic bone cement (Heraeus, Hanau, Germany), mixed with tobramycin 4.8 g and vancomycin 2 g. Vasso et al[11,45] used 4 g of vancomycin plus 2.4 g of tobramycin per 40 g of cement, although most of TKAs of those series were infected by multidrug-resistant bacteria.

According to the 2013 International Consensus Conference on PJI, even though the majority of the infections could be treated using vancomycin, gentamicin, and tobramycin, the antibiotics added to the cement should be individualized based on the antibiogram (if available).

Delayed reimplantation

After the first stage, intravenous and/or oral targeted antibiotics are generally administered for 6-12 weeks based on the recommendations of an infectious disease doctor[24]. After this period the second stage is performed. During this stage, a permanent prosthesis fixed with antibiotic-impregnated cement is implanted[12,34]. Reimplantation is performed when sufficient clinical, radiographic, and laboratory (CRP and ESR) evidence support the absence of an infection. The last ESR and CRP levels are taken no less than 2 weeks after antibiotic cessation[48]. Anyway, some factors could affect the reliability of these biomarkers: the low virulence bacteria, the antibiotics in the cement spacer, and recent systemic antibiotic administration. Therefore, some authors have proposed obtaining repeated cultures by knee aspirations after antibiotic cessation and before reimplantation to determine whether the persistent infection is still present[48]. However, this practice is not considered the standard of care, considering that repeated cultures are fraught with sampling errors and high false negative rates and poor sensitivity. In fact, the 2013 International Consensus Conference on Periprosthetic Joint Infection[63] do not recommend this practice. Recently, it has been introduced a combined measurement of synovial fluid CRP and Alpha-defensin protein levels. In fact, while synovial fluid α-defensin test alone demonstrated a sensitivity of 97% and a specificity of 96% for the diagnosis of periprosthetic joint infection, the combination of this test with CRP demonstrated a sensitivity of 97% and a specificity of 100% for the diagnosis of periprosthetic joint infection[50].

To date, aspiration of the knee joint and nuclear medicine modalities are not routinely performed before the second stage. In patients with rheumatoid arthritis and chronic inflammatory diseases, laboratory markers might not normalize; therefore, their substantial improvement over time helps to guide the timing of reimplantation. Other factors that can be used to guide the decision to reimplantation, in these patients, is the wound appearance and the results of the aspirate before reimplantation[12]. In case of suspected persistence of the infection, cement spacer should be revised (multiple-stage reimplantation)[51].

At the time of reimplantation, the spacer and the cement are carefully removed. Tissue specimens are sent for microbiologic and histopathologic examinations. If the intraoperative frozen section indicates a state of persistent acute inflammation, an antibiotic-loaded cement spacer should be reapplied[48,52]. Afterwards, soft tissues and the bone surfaces are carefully debrided. Finally, a modular revision implant system is generally used to manage bone loss and laxity[53]. The revision prosthesis is fixed with vancomycin-loaded cement. Bone defects can be managed with structural allografts, metal augments, porous tantalum cones and mod-

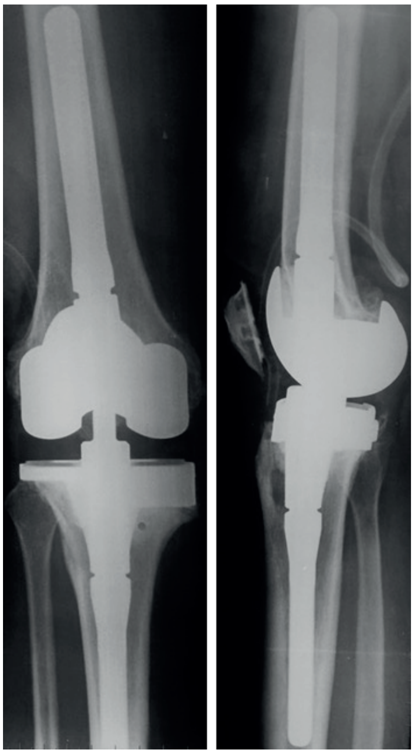

Figure 3. In this case at reimplantation a semi-constrained (CCK) prosthesis was implanted, with a medial tibial metal augment and femoral and tibial modular press-fit stems.

ular press-fit stems[54] (Figure 3). After reimplantation, intravenous antibiotics are administered for at least 4-5 days and stopped if the intraoperative cultures result negative. If intraoperative cultures are positive, instead, antibiotics have to be continued for at least 6 weeks, based on recommendations of the infectious disease doctor[12,26,55].

Our experience

In a recent retrospective case series of 46 infected TKAs, we reported that two-stage revision with an articulated cement spacer following a periprosthetic knee infection provided a significant long-term improvement of preoperative clinical and functional scores and therefore a durable revision TKA[45]. An articulated spacer, molded in the surgery room, was implanted in 46 consecutive patients. Patients were followed for a median period of 12 (range 6 to 16) years. The procedure was successful in controlling the infection in 91.3% of patients. A failure occurred in four patients. In the 42 patients with a successful two-stage revision, the median IKS knee and function scores were 36 (range 16 to 56) points and 25 (range 15 to 35) points, respectively, before the operation, and 76 (range 52 to 94) points and 70 (range 55 to 90) points ($p < 0.001$) at the latest follow-up. The median ROM increased from 80 (range 60 to 110) degrees preoperatively to 115 (range 100 to 128) degrees ($p < 0.01$) at the latest follow-up. After the first stage, all 46 knees had anatomical and functional integrity of the extensor apparatus. No severe wear or breakage of the cement spacer was reported, no patient presented massive radiographic osteolysis or clinical signs of severe knee synovitis. Spacer removal was easy in all cases.

Discussion

Two-stage reimplantation has been reported to be the most successful treatment of TKA infections. The strategy of using an antibiotic-loaded cement spacer and intravenous antibiotics with delayed revision arthroplasty is actually considered the state-of-the-art with a reported success rate of 88-96%[2,5,18-27,46]. Recently, the two-stage protocol has been reported as a viable option also for patients with a periprosthetic knee infection by resistant organisms[45]. On the other hand, open debridement with polyethylene exchange and single-stage reimplantation have been reported effective only in selective case series involving acute infections by low-virulence organisms[17].

Borden first used a two-stage protocol with block spacers following TKA infection, reporting a 90% success rate[56]. Wilde and Ruth alike reported a 90% success rate using the same protocol[57]. Similarly, Booth and Lotke reported a 96% success rate in eradicating infection[36], while Whiteside likewise reported a 94% success rate in a series of 33 infected knees using a block spacer[58]. More recently, Emerson et al[30] reported the results of 26 patients treated with a block spacer and of 22 patients treated with an articulated spacer. The reinfection rates were similar between the two groups, but patients treated with the articulated spacer had a significantly better average range of movement at follow-up of 36 months (107.8° *versus* 93.7°). Similarly, Fehring et al[31] reported the results on the use of molded articulated spacer *versus* block spacer. The author reported a reinfection rate of 12% with the use of a block spacer and a 7% reinfection rate with an articulated spacer. Furthermore, the author reported no cases of bone loss in patients treated with an articulated spacer, instead of the 60% observed among patients treated with the static one. Jones et al[39] used an articulated cement-implant composite spacer in 23 patients with infected TKA. The original femoral component, previously cleaned and resterilized in the autoclave, and a new tibial polyethylene of appropriate size were used as an articulated spacer; these components were fixed to the bone with antibiotic-loaded cement. They also used calcium sulphate-antibiotic beads, placed intramedullary and in the medial and lateral gutters and suprapatellar pouch. They obtained the eradication of infection in 22 (96%) patients at a mean follow-up of 13 months. Cuckler[34] used the same protocol to treat 44 chronic total knee infections. The sterilized femoral component and tibial polyethylene were coated with impregnated-antibiotic bone cement. The 95% of the patients were allowed to full weight bearing without assistive devices, and the mean range of motion was 110°. The author reported only 1 failure with a recurrent infection. The author emphasized the easy of the re-implantation with compliant soft tissues, without requiring tubercle osteotomy and quadriceps snip or turndown to increase the exposure.

A recent study[19] identified four potential risk factors that may predict treatment failure following two-stage revision for chronic knee infected knees: body mass index ≥30 kg/m^2 ($p < 0.001$), operative time > 4 hours ($p < 0.001$), gout ($p = 0.001$), and the presence of Enterococcus species during resection arthroplasty ($p = 0.002$). This finding may be useful when counseling patients regarding the treatment success and prognosis of two-stage reimplantation for infected TKA Some authors[59] reported that a positive bacterial culture during re-implantation is associated with poor outcomes and subsequent implant failure.

Only a few works have reported the long-term clinical and functional outcomes of two-stage reimplantation with articulated spacers. At a median follow-up of 12 years, Vasso et al[45] reported a 91.3% infection eradication rate, with a significant improvement of the functional outcomes in most of the patients. At the latest follow-up, patients judged the result as excellent or good in 84.4% of cases and fair in 15.6%. 86.9% of the entire cohort reported no pain, while 13.1% mild discomfort. Castelli et al[60] retrospectively reviewed 50 patients with infected TKA who underwent a two-stage exchange arthroplasty using an articulating preformed spacer. The two-stage protocol was successful in controlling the infection in 92% of patients at a median follow-up of 7 (range 2 to 13) years, whereas clinical and functional scores and ROM significantly improved. In this series, 29% of patients reported mild discomfort at the latest evaluation. Similarly, Gooding et al[61] retrospectively reviewed 110 knees that underwent two-stage reimplantation with the articulated PROSTALAC spacer with a mean follow-up of 9 (range 5 to 12) years. Mean clinical, functional and patient satisfaction scores significantly improved at last evaluation, although preoperative and postoperative knee flexion values of the patients were similar. Optimal functional results were probably due to the mechanical properties of the PROSTALAC knee spacer that has two cement components, femoral and tibial and a small metallic inset prosthesis that provides a low-friction articulation. However, the presence of this metal component between femoral and tibial cement components could probably explain the relatively high (13%) incidence of infection persistence of the initial two-stage approach. Finally, Hofmann et al[24] treated 50 consecutive patients with an infected TKA through a two-stage revision with an articulating spacer. After a mean follow-up of 6 years (range 2 to 12), clinical scores and ROM significantly improved, with 90% of good to excellent functional results among infection-free patients. The authors also reported bone stock preservation, no soft tissue and wound problems, and easier reimplantation with a surgical time equal to the primary TKA.

Conclusions

The strategy that involves the use of cement spacer, intravenous antibiotic therapy and revision total knee arthroplasty is nowadays considered the gold standard for the management of the periprosthetic knee infection. This treatment, generally chosen only for chronic knee infection, is actually considered the first choice also in case of acute infections and especially in the presence of multidrug-resistant bacteria.

Conflict of Interests

The authors declare that they have no conflict of interest.

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