

# USE OF ANTIBIOTIC SPACERS FOR KNEE ENDOPROSTHESIS INFECTIONS TREATMENT

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## ABSTRACT

**Objective:** The aim of this study is to evaluate the use of cement spacers impregnated with antibiotics for the treatment of infections in the nonconventional endoprostheses of the knee. **Methodology:** We have treated seven patients since 2004 (of which six were submitted to surgery in our service and one patient had been submitted to a primary tumor surgery in another removal service) with deep infection in knee tumor prosthesis. All patients were submitted to endoprosthesis removal and reconstructed with antibiotic cement spacer. All patients were monitored both clinically and by lab tests as for monitoring the evolution, being considered able for reviews after 6

(six) months without infections signs. **Results:** We have noted a small predominance of infectious processes on the prosthesis inserted on proximal tibia as compared with distal femur (57.1% x 42.9%). The mean follow-up time of patients was 68.2 months. During the follow up, one patient died as a result of the root disease. Six patients out of seven were regarded as cured and one persisted with infection signs and symptoms. **Conclusion:** The results obtained up to date have motivated us to continue using this method of treatment.

**Keywords:** Prosthesis. Neoplasms. Infection. Bone cements. Osteosarcoma.

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## INTRODUCTION

Nonconventional knee endoprostheses are largely employed in reconstructions after bone tumor resections around the knee. This kind of implant presents the same complication rates as the conventional knee prostheses.

The name 'nonconventional endoprosthesis' is due to the fact that the osteotomy for its placement is more extensive than in the cases of conventional prostheses. In conventional knee prostheses, osteotomy reaches the distal metaphyses of the femur and proximal metaphyses of the tibia, being usually performed with the aid of metaphyseal templates. On the other hand, in nonconventional endoprostheses, there is no rule of thumb for the osteotomy location. Bone resection varies according to the size of the tumor and the oncologic margin of the lesion.

The bone affected by tumor, in the large majority of times, is submitted to a diaphyseal osteotomy. This kind of diaphyseal resection gives rise to a large bone failure, requiring the use of an implant enabling bone length and its perfect joint alignment reestablishment. Nonconventional endoprostheses were introduced, thus, as a method for reconstructing bone failures resulting from the resection of musculoskeletal tumors.<sup>1-4</sup>

The major acute complications of this kind of surgery are infection,

dehiscence, collections formation, such as hematoma or seroma and deep venous thrombosis.<sup>3,5</sup> At late stages, this kind of procedure may present other complications, such as aseptic loosening of the implant, a broken component of the endoprosthesis, periprosthetic infection, and septic loosening of the implant. In addition to those, local recurrence of tumor may occur, with or without implant loosening.<sup>4,6</sup>

Peri-prosthetic infections are usually symptomatic. The classical signs of local heat, redness, and pain may be present. Fistulization of collections is a common event in these cases, with serous, blood red cells or purulent leakage. In some cases of late infection we didn't find at first any classical inflammatory signs. The patient may evolve with pain at prosthesis site and, at the X-ray evaluation, signs of components loosening can be visualized or not.<sup>7</sup> These cases constitute a greater challenge for diagnosis.

The key laboratory changes are the leukogram modification (with an infectious pattern), increased hemosedimentation speed and increased serum reactive C protein. These tests, in addition to support the diagnosis, serve as parameters of the therapeutic response during patient's follow-up. On X-ray tests, we can find endoprosthesis loosening (lysis around the cement) and deep peri-prosthetic collections.

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The classical treatment for peri-prosthetic infections relies on therapy with antibiotics driven by results of cultures and antibiograms and by the removal of the infected endoprosthesis. In cases of infection around nonconventional endoprostheses, the bone failure found after the implant removal requires a reconstruction method.

Many authors recommended amputation as a definitive method for fixing infections around knee endoprostheses.<sup>8</sup> Reconstruction techniques are based on joint arthrodesis after bone transportation with the method by Ilizarov. Another technique fosters transportation with the use of linear fixators and subsequent arthrodesis. Arthrodesis *in situ* may also be provided, causing a dramatic shortening the limb. In this case, there is no bone transportation, and the limb becomes quite shorter.

Following the same treatment approach as in peri-prosthetic infections for knee total arthroplasty, the use of acrylic cement spacers with antibiotics was suggested. In this treatment approach, the spacer provides, in addition to its mechanical function, a therapeutic antibacterial function, with the local release of antibiotic agents.

Since the bone failure found after UCE removal is quite large, using a cement spacer only is not enough for providing an appropriate mechanical stabilization. With the purpose of improving mechanical stabilization, the technique using a cement spacer with a stiff nail inside it was developed. Thus, the cement with antibiotics makes contact with bone and muscular bed, and the nail at the assembly core allows a better functional stabilization.

Once the spacer system is assembled, the patient is clinically treated (for a variable period of time) with appropriate antibiotics (based on culture and antibiogram results of materials collected at the peri-prosthetic region), and, after total remission of signs and symptoms, and upon the stabilization of laboratory parameters, the spacer can be removed and replaced by a new NCE.<sup>9,10</sup>

The objective of this study is to present a method for treating deep infections in patients submitted to tumoral resection and reconstruction with nonconventional knee endoprosthesis.

## MATERIALS AND METHODS

Between January 1st, 1990 and December 31st, 2006, 283 surgeries for inserting an nonconventional knee endoprosthesis after tumoral resection (patients with tumors on distal femur and proximal tibia) have been carried out in our service.

During follow-up, 24 (twenty-four patients – 8.48%) patients evolved with deep infection of the endoprosthesis site. Up to 2004, the patients with deep peri-prosthetic infection were treated by removing the endoprosthesis and with external fixation (for elongation or arthrodesis) or with amputation of the limb. From 2004 on, we started to operate the patients by removing the endoprosthesis followed by reconstruction with acrylic cement spacer with antibiotics. The case series of this study, thus, consists of 6 (six) patients with peri-prosthetic infection operated from 2004 on, added by a patient submitted to tumoral resection surgery and reconstruction with nonconventional endoprosthesis whose surgery was performed in another hospital, being subsequently followed up in our outpatient service. When this patient was referred to our outpatient facility, he already presented with

deep infection, making use of oral antibiotics for 3 months, and he had already been submitted to surgical debridement on the endoprosthesis site.

The studied patients, as approved by UNIFESP/EPM's Committee of Ethics, consisted of 2 males (28,6%) and 5 females (71.4%). The mean age when the infection was diagnosed was 35.9 years (range: 11-68 years). Concerning the baseline disease, 6 (six) patients had osteosarcoma (3 metastatic and 3 non-metastatic), and 1 patient presented giant cells tumor (GCT) as a baseline pathology. The six patients affected by osteosarcoma were submitted to a neo-adjuvant and adjuvant chemotherapy approach (according to the protocol in force at the moment of diagnosis). The patient with GCT had a tumor on distal femur with extra-bony lesion, showing resection with wide margins and reconstruction with nonconventional knee prosthesis. This patient had 2 episodes of local recurrence, and he was submitted to resection of the recurrences around the prosthesis. No patient received radiotherapy as adjuvant treatment.

All patients received therapy with antibiotics (oral and endovenous) when diagnosed with infection. During follow-up, all patients were submitted to at least one surgical debridement surgery but not removing prosthesis components. All patients were followed up through leukograms, hemosedimentation speed and reactive C protein tests. All patients received therapy with specific antibiotics after culture tests and antibiograms collected intraoperatively at debridement procedure.

All patients with persistent infection after one surgical debridement event and receiving antibiotic therapy for at least 6 weeks (specific antibiotic therapy) were regarded as eligible for endoprosthesis removal and limb reconstruction with modeled spacers with nail and cement with antibiotics. In our case series, all patients with infection after 2004 were regarded as eligible to treatment.

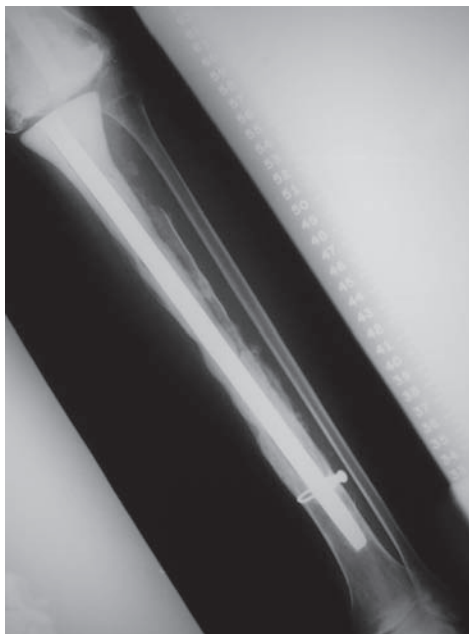
The seven patients were submitted to a new surgical procedure through the same port used for tumor resection. In cases where fistulas were present, fistulectomy was carried out with resection of the whole scar (ellipse resection). By performing the endoprosthesis approach, new culture and antibiogram samples were collected in order to guide the postoperative antibiotic therapy approach. The endoprostheses were removed (all the components) and all the cement previously used was removed. We performed an extensive debridement of the necrotic tissues around the endoprosthesis. At the bone approach, a careful curettage of the femoral and tibial medullar was performed. After the debridement, the area was cleaned with saline solution 0.9% (at least 15 liters were used in each procedure).

For reconstruction, femoral nails were used wrapped with cement with antibiotics. In all patients, the Simplex<sup>®</sup> brand acrylic cement with antibiotics (Tobramycin) was used.

In order to determine infection control, we employed clinical and laboratory parameters. Clinically, we saw total healing of the surgical wound, absence of fistulas and leakages, and absence of flogistic signs. Concerning laboratory analysis, we saw the reduction of Hemosedimentation speed, reactive C protein, and leukogram levels to normal parameters. We regarded a patient as able to endoprosthesis replacement when the clinical and laboratory parameters remained at normal levels for 6 (six) months (Figures 1 and 2).



**Figure 1 -** Acrylic cement spacer with antibiotics around a metal nail (single nail).



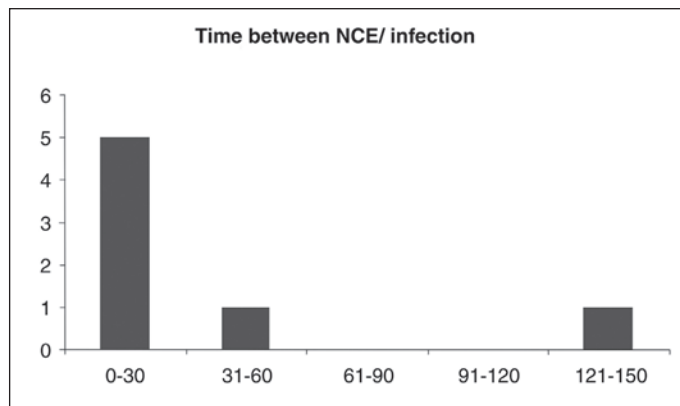
**Figure 2 -** Acrylic cement spacer with antibiotics around a metal nail (double nail).

## RESULTS

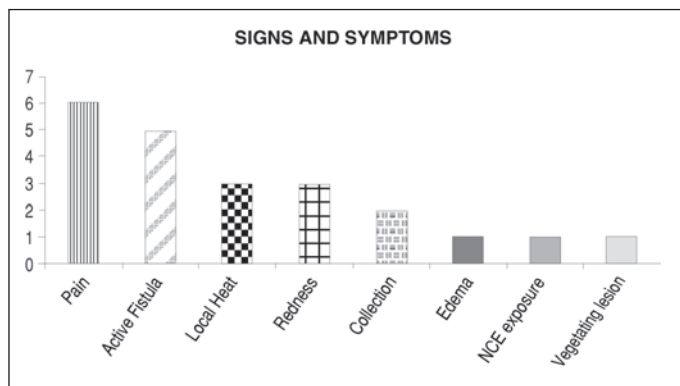
We found a subtle prevalence of the incidence of infectious process on prosthesis implanted in patients with proximal tibial tumors when compared to the baseline location of the tumor on the distal femur (57.1% of the cases showed a baseline tumor on proximal tibia, while 42.9% on the distal femur).

Concerning the endoprosthesis model employed, in 6 patients a nonconventional custom-made prosthesis was used, and, in one case, this was an extensible-type endoprosthesis. This was the only patient in the case series presenting with a partial knee prosthesis (only the femoral component). The size of the endoprosthesis body was, in average, 142.9 mm.

Concerning the anatomical-pathological report, all patients were submitted to resections with wide margins and presented free margins. The patients presented the first signs and symptoms corresponding to infectious processes within a period that ranged from 3 to 127 months after the endoprosthesis insertion surgery (mean: 32.1 months, and median: 24.8 months (Figure 3)). The signs and symptoms found in our study were the following: pain (n=6, 85.7% of the patients), active fistula (n=5, 71.4% of the patients), local heat (n=3, 42.9% of the patients), redness (n=3, 42.9% of the patients), palpable liquid collection (n=2, 28.6% of the patients), skin lesion and prosthesis exposure (n=2, 28.6% of the patients) and diffuse edema on the limb (n=1, 14.3% of the patients). (Figure 4)



**Figure 3 -** Evolution time (days) between the endoprosthesis insertion and the onset of infection according to the number of cases.



**Figure 4 -** Signs and symptoms of the infectious picture of patients by frequency order.

All patients were submitted to at least one surgical procedure for debridement and surgical cleaning previously to the indication of endoprosthesis removal. One patient (the one diagnosed with giant cell tumor) was submitted to two surgical cleaning procedures previously to the indication of endoprosthesis removal.

The time elapsed between clinical diagnosis of infection and endoprosthesis removal ranged from 2.3 months and 88.8 months (mean: 35.2 months, and median: 12.1 months). The time elapsed between the 1st surgery and the endoprosthesis removal ranged from 13.3 months to 129.3 months (mean: 67; median: 69.6 months).

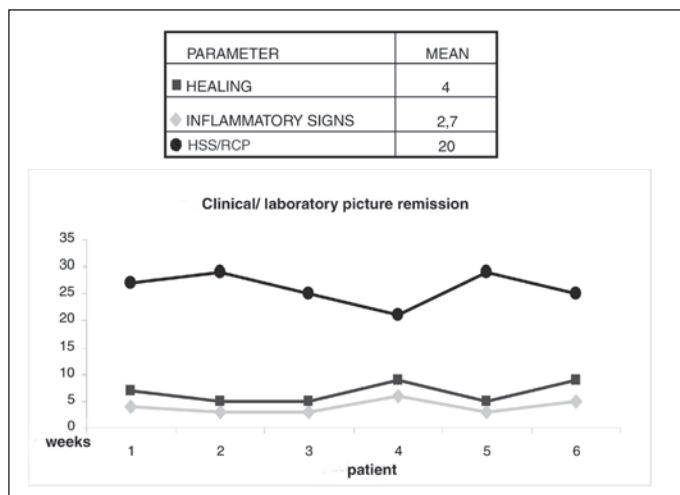
Acrylic cement spacers with antibiotics may be placed for blocking

knee joint (single nail) or with two nails (assembling 2 separate spacers, one for the femur and another for the tibia), allowing a pseudoarticulation between spacers (double nail). In the case series presented here, 2 (two) (28.6%) double-nail spacers, and 5 (five) (71.4%) single-nail spacers were inserted. All spacers were assembled with Simplex® cement with Tobramycin.

For the screening of etiologic agents, cultures were collected intraoperatively from the endoprostheses beds. The identified etiologic agents were the following: *Staphylococcus aureus* in 4 cases (57.1%), *Acinetobacter* in 1 case (14.3%), *Streptococcus sp.* in 1 case (14.3%), and *Enterobacter* in 1 case (14.3%). All patients received postoperative therapy with specific antibiotics according to the culture and the antibiogram. Thus, 4 patients (57.1%) were treated with ciprofloxacin, 2 patients (28.6%) were treated with vancomycin, and 1 patient (14.3%) was treated with sultamycin. Antibiotic therapy time ranged from 2 to 33 months (mean: 5.5 months) after endoprosthesis removal.

The most prevalent objective clinical sign is the presence of active fistula. Additionally to the fistula, classical inflammatory signs were assessed (heat, redness, edema and pain), as well as laboratory parameters. (Figure 5). Of the 7 patients assessed, 6 (85.7% of the cases) evolved with clinical and laboratory parameters improvement, while one patient didn't present improvement and evolved with persistent infectious process.

For the 6 patients responding well to the recommended treatment, the mean time for fistulas closing was 4 weeks (3-24 weeks). Inflammatory signs have also improved, returning to normal levels within 4 weeks (3-24 weeks), while the mean time for HSS and reactive C protein normalization was 20 weeks (12-100 weeks). (Figure 5)



**Figure 5 – Correlation between time for remission of the clinical picture and inflammatory signs.**

The mean follow-up time is 68.2 months (13.9 to 120.9 months). One patient was submitted to spacer removal and endoprosthesis replacement. Currently, this patient shows no signs of infection on the new endoprosthesis. Concerning the other 6 patients, one is waiting for endoprosthesis replacement, one died as a result of the baseline disease, and the remaining 4 did not accept to be submitted to a new surgical procedure at risk of perpetuating

the infectious process. These patients remained with the spacers, and no major complication was found so far.

Of the 7 (seven) patients submitted to spacer insertion, 6 (six) evolved with shortening of the affected limb, which ranged from 1.5 to 8 cm (mean: 3.2 cm).

Taking only the patients who survived throughout follow-up into account, we have a cure rate of 83.3% with the described method. Due to the small sample, we couldn't design an appropriate multifactorial analysis to determine which variables present a stronger impact for peri-endoprosthetic infection treatment.

## DISCUSSION

Infection is one of the most feared complications occurring in orthopaedic surgeries. Tumor resection surgery and the reconstruction with NCE present a risk of infection ranging from 5% to 35%. Such high incidence occurs mainly because of oncologic patients' characteristics, which, many times, have diseases leading to immunosuppression. Furthermore, chemotherapy and radiotherapy play an immunosuppressant role (both local and systemic), increasing the risks of infection.

On the other hand, tumor resection surgeries requiring reconstruction with NCE are major procedures, showing a lengthy surgical time and leading to a higher risk of infections.

Since the 1970's, many authors have tried to determine which would be the best method for peri-prosthetic infection treatment. The first treatment method described for treating infections in knee total arthroplasties was the plain surgical cleaning, recommended to any type of infection around implant materials.<sup>11</sup> Brodersen et al.<sup>12</sup> were the first to describe, in the 1970's, knee arthrodesis as a method for treating arthroplasty failures. In their series of 45 patients, 40 presented infection as the root cause of implant failure, being submitted to knee arthrodesis.

Phillips et al.<sup>13</sup> have also proposed knee arthrodesis after an implant removal, but using the Hoffman's external fixator. With this technique, they were able to achieve a faster union and less shortening compared to internal techniques.

Insall<sup>14</sup> was the first author to write a review article about the peri-prosthetic infections theme. The author considered surgical cleaning as imperative, as well as the implant removal and endovenous antibiotic therapy. Insall was also the first to suggest the review in two steps. After the surgery, the patient would be on endovenous antibiotic therapy for six weeks, and only after that period a new surgery for inserting the new prosthesis would be indicated.

Poss et al.<sup>15</sup>, in the 1980's, assessed 4240 patients in an attempt to determine which would be the most important groups at risk of infection around the knee. In their text, the authors discuss that the pathologies leading to immunosuppression are the key risk factor for infection around knee total arthroplasty, followed by patients with previous revision procedures. Bliss and McBride<sup>16</sup> emphasized, at the time, the importance of the full prosthesis coverage with myocutaneous flaps.

In the 1980's, Borden and Gearen<sup>17</sup> suggested a treatment protocol for knee total peri-prosthesis infection. The methods described by the authors consisted of primary review of the prosthesis, aggressive and isolated surgical cleaning, and of the review in two steps.

Wilde and Ruth<sup>18</sup> pioneered the description of a review method in two steps with the use of an acrylic cement spacer with antibiotics. In that initial study, the authors removed the prosthesis and kept the patient under endovenous antibiotic therapy for 4.2 weeks, and removing the spacer and replacing arthroplasty. Morrey et al.<sup>19</sup>, in 1989, recommended that, in acute infections, aggressive debridement and surgical cleaning should be made, which could cure the infection in up to 80% of the cases.

Wirganowicz et al.<sup>3</sup> assessed the causes of nonconventional endoprosthesis failures. The authors assessed 278 prostheses, finding an infection rate of 13%. More recently, Gosheger et al.<sup>20</sup> assessed the effects of a silver layer on the endoprosthesis as a way to reduce the rate of infections. In an experimental study, the authors concluded that silver could reduce the risk of periprosthetic infection from 47% (control group) to 7%.

Since literature does not describe which would be the best method

for treating deep infections around nonconventional knee endoprotheses, we found support on treatment techniques for infections around knee total arthroplasties. Our primary concern was maintaining a conservative surgery on the limb. The indication of surgical cleaning previously to the endoprosthesis removal is described, which can lead to resolution of the infectious process without requiring a more aggressive procedure.

## CONCLUSION

Based on our findings, we couldn't determine the key positive predictive factors for a better evolution in cases of infection around nonconventional endoprotheses. However, we conclude that the method employed shows good results with great chances of curing the infectious process.

We also conclude that the major complication resulting from the method is dysmetria of the affected limb.

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