Risk Factors Related to Poor Outcomes in the Treatment of Non-conventional Periprosthetic Infection*

Fatores de risco relacionados à má evolução no tratamento da infecção periprótese não convencional

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Abstract

Objectives To identify the main risk factors related to poor outcomes after the treatment for periprosthetic infection.

Materials and Methods Medical records from 109 patients who underwent non-conventional endoprosthesis surgeries (primary and revision procedures) from January 1, 2007, to December 31, 2018, were retrospectively evaluated. In total, 15 patients diagnosed with periprosthetic infection were eligible to participate in the study. Variables including gender, age at diagnosis, affected bone, surgery duration, white blood cell (WBC) count before endoprosthesis placement, urinary tract infection during the first postoperative year, and time elapsed from endoprosthesis placement to infection diagnosis were related to outcomes using the Fisher exact test (for the bicategorical variables) or analysis of variance (ANOVA, for the tricategorical variables). The mean times from diagnosis to final outcome were compared using the Student *t*-test.

Keywords
- prosthesis and implants
- sarcoma
- infections
- osteosarcoma
- amputation
- debridement

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Results These risk factors did not show a statistically significant correlation with the outcomes. The data revealed a trend towards a difference between the mean time for the onset of infection and the final outcome. Due to the limited sample, we believe that studies with larger cohorts can prove this trend.

Conclusion We identified that the time from endoprosthesis placement to the onset of the symptoms of infection tends to be related to the outcome and evolution of the patient evolution during the treatment for periprosthetic infection. Although apparently correlated, other associated factors were not statistically linked to poor treatment outcomes.

Resumo

Objetivos Identificar os principais fatores de risco relacionados à má evolução no tratamento da infecção periprótese.

Materiais e Métodos Foram avaliados de forma retrospectiva os prontuários de 109 pacientes submetidos a cirurgias de endoprótese não convencional (primárias e revisões), no período de 1° de janeiro de 2007 a 31 de dezembro de 2018. Destes, 15 pacientes diagnosticadas com infecção periprótese foram elegíveis para a participação no estudo. As variáveis sexo, idade no diagnóstico, osso acometido, duração da cirurgia, contagem de leucócitos no pré-operatório, infecção do trato urinário no primeiro ano de pós-operatório, e tempo decorrido entre a colocação da endoprótese e o diagnóstico da infecção foram relacionadas aos desfechos utilizando o teste exato de Fisher (variáveis bicategóricas) e A análise de variância (*analysis of variance*, ANOVA, em inglês) (variáveis tricategóricas). As médias de tempo entre diagnóstico e desfecho foram comparadas pelo teste *t* de Student.

Resultados Os fatores de risco avaliados não demostraram correlação estatisticamente significativa com os desfechos. Os dados demonstram haver tendência de diferença entre a média de tempo do aparecimento do processo infeccioso e o desfecho final do paciente. Devido à amostra limitada, acreditamos que estudos com coortes maiores possam comprovar essa tendência.

Conclusão Identificamos que o tempo entre a cirurgia de colocação da endoprótese e o aparecimento dos sintomas de infecção tende a ter relação com o desfecho e a evolução do paciente no tratamento da infecção periprótese. Os demais fatores associados, apesar de aparentemente relacionados, também não se mostraram estatisticamente relacionados à má evolução no tratamento.

Palavras-chave
- próteses e implantes
- sarcoma
- infecções
- osteossarcoma
- amputação
- desbridamento

Introduction

The survival of patients with malignant bone tumors has increased due to advances in chemotherapy and radiation therapy. Although biological reconstructions are preferred, many situations require non-biological techniques and non-conventional endoprostheses. Like any conventional arthroplasty, endoprostheses are susceptible to failure and infection.[1,2]

Prosthesis failures result from aseptic loosening, soft-tissue failure, structural failure, tumor progression, and infection.[3] Endoprosthetic infection is one of the main complications of this type of surgery, with a reported incidence of 2.0% to 19.5%.[4]

The risk of developing infection differs depending on the location of the primary tumor. Resections around the knee (proximal tibia and distal femur) present an increased risk of infection compared to those around the humerus.[5]

Periprosthetic infection is suspected based on the clinical picture. An ultrasound scan can detect periprosthetic collection, whereas radiographs may show signs of implant loosening. The main laboratory findings include alterations in the white blood cell (WBC) count (revealing an infectious pattern), increased rate of erythrocyte sedimentation, and elevated serum levels of C-reactive protein.[6]

Several studies[3–5] recommend as diagnostic criteria the presence of at least one of the following: 1) growth of the same organism in two or more samples of synovial fluid or peri-implant tissues, or purulent secretion at the implant site or synovial fluid; 2) signs of acute inflammation on the histopathological examination of peri-implant tissues; or 3) presence of a fistula communicating with the endoprosthesis.[4]

The most frequently identified pathogens in cultures are coagulase-negative staphylococci (30% to 43% of the cases), followed by *Staphylococcus aureus* (12% to 23%), mixed flora (10% to 11%), streptococci (9% to 10%), gram-negative bacilli (3% to 6%), enterococci (3% to 7%), and anaerobes (2% to 4% of the cases).[7–10] There is a relationship between the topography of the endoprosthesis and the pathogens. For instance, *Propionibacterium acnes* is the main cause of postoperative infection in shoulder endoprostheses, warranting further tests to isolate the causative organism and increase the chances of cure.[7,11]

Biofilm is the main factor hindering the treatment of implant infection. It is defined as a set of bacteria encapsulated within their own polymeric matrix; when reaching a critical mass on the contaminated implant, biofilms induce an inflammatory reaction in their host which can ultimately lead to implant failure. Bacteria within biofilms are significantly less susceptible to antibiotics, host defense, and antiseptic agents, making treatment more difficult. Since biofilms lead to implant failure, the clinical options are quite limited and involve suppression with antibiotics for a long period of time or surgical revision, resulting in major morbidities and even death.[8]

The incidence of periprosthetic infection is higher among patients undergoing tumor resection than in those submitted to arthroplasty for non-oncological causes.[9,11,12] This is due to numerous differences, such as the larger surface area of implants, the larger approach, the longer surgical times, higher blood loss, dead space, chemotherapy-related immunodeficiency, radiotherapy, poor soft-tissue conditions, and extra-articular joint resection.[10,13,14]

Tumor location is also important, with the proximal tibia and pelvic endoprosthesis as risk factors for endoprosthetic infections. Due to their technical difficulty, pelvic surgeries have prolonged surgical times; the proximal tibia is susceptible to infection due to the difficulty in achieving good soft-tissue coverage.[9]

The literature correlates peri-implant infection with factors such as age, atopic dermatitis, diabetes, obesity, rheumatoid arthritis, smoking, history of infection, male gender, dehiscence, and hematoma.[3,13] However, there is no definition of which factors are actually associated with patient evolution after the treatment.

The present study aimed to identify the main risk factors related to poor outcomes after the treatment for periprosthetic infection.

Materials and Methods

Medical records of 109 patients who underwent non-conventional endoprosthesis surgeries (primary and revision procedures) from January 1, 2007, to December 31, 2018, were retrospectively evaluated. In total, 16 patients were diagnosed with periprosthetic infection. In one of them, the initial surgery and infection diagnosis had been performed at another service; as such, this patient was removed from the statistical analysis, leaving a group of 15 subjects (13.7%) with periprosthetic infection.

The present study consisted in a retrospective analysis of medical records from patients diagnosed with periprosthetic infection and treated at our institution. It was approved by the Ethics in Research Committee and registered at Plataforma Brasil under number CAAE 12665419.2.0000.5505.

Infection Diagnosis

The diagnosis of periprosthetic infection was based on a combination of classic signs and symptoms suggestive of an active infectious condition: pain around the prosthesis and/or inthe limb without any other diagnosable cause, increased temperature compared to that of the contralateral limb, local hyperemia, edema, and fever.

After clinical suspicion, all patients underwent an ultrasound scan which revealed evidence of fluid collection around the endoprosthesis. We routinely collected blood for laboratory tests, including culture, WBC count, erythrocyte sedimentation rate, and C-reactive protein measurement to assist the diagnosis and evaluation of the treatment of the infectious condition.

Infection treatment

The patients were submitted to the treatment recommended by the protocol from our service, with surgical cleaning and early debridement of devitalized tissues within seven days of the clinical diagnosis of periprosthetic infection. Periprosthetic fluid samples were taken for culture during the surgical cleaning.

The intravenous antibiotic therapy started after the surgical cleaning. First-generation cephalosporins are often used until the culture results are available. Then, the treatment is directed according to the sensitivity of the isolated etiologic agent. Patients with no improvement in signs, symptoms, or laboratory findings within 15 days were referred to endoprosthesis revision.

The revision procedure was preferentially performed in two stages, using an acrylic cement spacer with antibiotics for 45 to 180 days, followed by spacer removal and the placement of a new non-conventional endoprosthesis.[6] All patients were informed about the alternative of limb amputation.

One patient underwent a single-staged revision with removal of the components of the endoprosthesis, new surgical cleaning and debridement, and placement of a new implant in the same procedure.[15]

After the endoprosthesis revision surgery, antibiotic treatment was sustained for three to six months, as indicated by the institutional infectious disease team. All patients were submitted to postoperative clinical and laboratorial follow-up to assess infection recurrence. Patients with recurrence were referred to limb amputation. ►**Table 1** shows the epidemiological data of the patients and characterizes them per time up to diagnosis and treatment type.

The treated patients were considered in remission when presenting no clinical signs and symptoms of infection and laboratory findings negative for active infection at the end of the study period (December 2018).

The patients were divided into three retrospective cohorts considering limb amputation as the primary outcome of the study. The first cohort consisted of patients with infection

Table 1 Epidemiological data of the patients and their characterization regarding the time until infection diagnosis and the treatment performed

Gender	N	%
Male	7	46.7%
Female	8	53.3%
Age		
Mean	20	
Minimum	10	
Maximum	31	
Standard deviation	7.2	
Diagnosis		
Osteosarcoma	12	80.0%
Ewing sarcoma	2	13.3%
Undifferentiated sarcoma	1	6.7%
Tumor location		
Femur	12	80.0%
Tibia	3	20.0%
Time from surgery to infection diagnosis		
$<$ 6 months	6	40.0%
6 to 12 months	2	13.3%
$>$ 12 months	7	46.7%
Treatment performed		
Surgical cleaning alone	5	33.3%
Revision in two stages using an acrylic cement spacer with antibiotics	9	60.0%
Revision in a single stage	1	6.7%

remission and limb preservation after treatment (with endoprosthesis revision or not). The second cohort consisted of patients with unsuccessful infection control who underwent limb amputation. And the third consisted of patients submitted to surgical cleaning alone.

The following variables were evaluated as infection-related factors: gender (male or female), age ($\leq$15 years or $>$ 15 years), diagnosis (osteosarcoma or other tumors), affected bone (femur or tibia), duration of endoprosthesis placement surgery ($\leq$300 minutes or $>$ 300 minutes), WBC count immediately before the placement of the endoprosthesis (leukopenia: $\leq$ 3,000 WBC; no leukopenia: $>$ 3,000 WBC), urinary tract infection within the first year of the placement of the endoprosthesis (presence or absence of infection), and time elapsed from endoprosthesis placement and infection diagnosis ($\leq$ months, from 6 to 12 months, and $>$ 12 months).

The Fisher exact test was performed assuming a *p*-value of 0.05 to assess the significance of the association of bicategorical variables, since the groups were small. Analysis of vsriance (ANOVA) was used for the tricategorical variables. For each variable, the null hypothesis (H0) was that there was no difference between the categories and amputation as an outcome.

The average times of the three groups of patients (revision of the endoprosthesis with limb preservation, limb amputation, and surgical cleaning alone) were assessed separately and compared using the Student *t*-test.

Results

Of the 15 patients, 3 presented persistent infection and underwent limb amputation. The effectiveness of the treatment protocol was of 80% for limb preservation.

None of the risk factors evaluated (gender, age, diagnosis, affected bone, duration of the endoprosthesis placement surgery, WBC count immediately before endoprosthesis placement, urinary tract infection within the first postoperative year, and time elapsed from endoprosthesis placement and infection diagnosis) was directly related to amputation in patients with periprosthetic infection.

►**Table 2** shows the variables studied, the incidences of amputation and preservation of, the values of the Fisher exact test for each variable, and the ANOVA results regarding the time between endoprosthesis surgery and infection diagnosis.

None of the patients who progressed to amputation showed early signs of infection (within 6 months). The average time for the onset of signs of infection in patients submitted to revision with limb preservation was of 710 days (range: 158 to 1,729 days); the average time among patients who progressed to amputation was of 1,246 days (range: 294 to 2,352 days); and, among those who underwent surgical cleaning alone, it was of 199 days (range: 11 to 784 days). ►**Table 3** shows the average period (in months) and the results of the Student *t*-test.

The data demonstrate a trend towards a difference between the mean time of onset of the infection and the final outcome (►**Figure 1**).

Discussion

Periprosthetic infection remains an important cause of complications and endoprosthesis failure. Failure, morbidity, and mortality are the most common results of this condition. Recent studies[16,17] indicate that infection increases the number of amputations after the placement of endoprostheses.

Some of the treatment methods for this complication include: debridement with cleaning and endoprosthesis retention; endoprosthesis revision in a single stage (in which the infected prosthesis is removed) followed by vigorous cleaning and placement of a new endoprosthesis; and revision in two stages using a cement spacer impregnated with antibiotics, followed by replacement in a second procedure. The spacer is removed when the patient's clinical and laboratory condition normalizes, and it is replaced by the new endoprosthesis. Finally, amputation is chosen after all other methods have failed to control the infectious disease, in an attempt to preserve the patient's life.

Among these methods, two-staged revision has shown the best outcomes. Our team has been using this treatment for more than 10 years, with good clinical and functional

Table 2 Variables studied, incidences of amputation and preservation of limbs, and statistical result

Variables	Limb preservation	Limb amputation	Statistical result
Gender			*Fisher exact test*
Male	6	1	*0.250*
Female	6	2	
Diagnosis			*Fisher exact test*
Osteosarcoma	9	3	*0.875*
Not osteosarcoma	3	0	
Affected bone			*Fisher exact test*
Femur	10	2	*0.533*
Tibia	2	1	
Preoperative leukopenia			*Fisher exact test*
> 3,000 white blood cells	6	2	*0.250*
< 3,000 white blood cells	6	1	
Urinary tract infection withing the first postoperative year			*Fisher exact test*
No	9	3	*0.875*
Yes	3	0	
Surgery duration			*Fisher exact test*
≤ 300 minutes	4	2	*1.037*
> 300 minutes	8	1	
Age			*Fisher exact test*
≤ 15 years	5	0	*1.750*
> 15 years	7	3	
Time from surgery to infection diagnosis			*Analysis of variance*
< 6 months	6	0	*0.269*
6 to 12 months	1	1	
> 12 months	5	2	

Table 3 Average time (in months) until infection and results of the Student *t*-test for each subgroup of patients

Status	Time until infection (months)	Student *t*-test
Revision with limb preservation	23.7	*0.027*
Limb amputation	41.5	*0.173*
Surgical cleaning alone	6.7	*0.247*

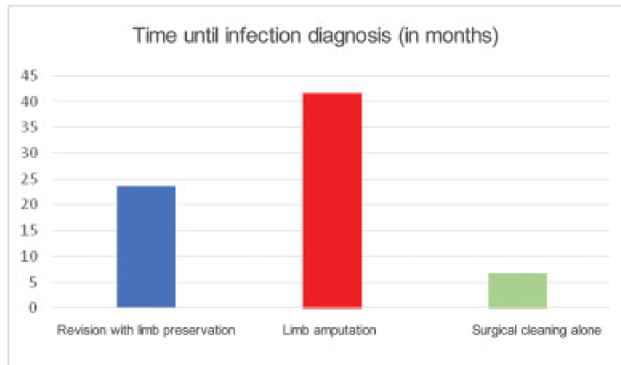

Fig. 1 Time until infection diagnosis (in months) for each subgroup of patients (revision with limb preservation, limb amputation, and surgical cleaning alone).

outcomes.[6] Its reported efficacy ranges from 63% to 100%, according to the literature.[18,19]

In the present series, patients diagnosed with osteosarcoma were the most affected by endoprosthesis-related postoperative infection. These data are consistent with those of the study by Racano et al.,[5] who identified osteosarcoma as the main related diagnosis, closely followed by Ewing sarcoma and chondrosarcoma.[5]

Even though a higher percentage of patients presented a late (over 12 months) onset of symptoms, those with earlier onset evolved more favorably. These data are not in line with the findings by Hardes et al.,[1] who reported that chemotherapy alone, as well as the timing, type, and virulence of the infection had no influence on the final outcomes.[1] Muratori et al.[16] observed a high number of infections in patients followed-up for more than 12 months after surgery, which is consistent with our findings.

Although the femur is the surgical site with the highest incidence of infection, the location of the disease, be it the femur or the tibia, is not related to the outcomes. Morii et al.[3] reported that the tibia, age < 30 years and the presence of a primary bone tumor are common findings in patients requiring revision surgeries due to infection.[3]

According to Hardes et al.,[1] debridement and implant retention with no stem replacement can be a good strategy for early infections (less than 6 months). However, like our team, these authors[1] believe that a two-staged revision results in better outcomes.

Among all treatments, amputation is seen as the last resort against infection. In the present study, the average time for amputation was of 41.5 weeks. Before this radical technique, cleaning with implant retention and its replacement with a spacer were attempted, followed by reimplantation as many times as required. However, in an important group of patients, amputation invariably presents itself as the last viable solution when other techniques fail.[20]

Study limitations

The greatest weakness of the present study is the low statistical power due to the small sample size. As this is a rare event, studies on non-conventional endoprosthesis surgeries have reduced samples. This bias can be corrected with multicenter studies and larger samples. Larger analyses may demonstrate the importance of other risk factors that were not identified in the present study.

Conclusion

The time elapsed from endoprosthesis placement to the onset of the symptoms of infection tends to be related to the outcome and evolution of the patient during the treatment for periprosthetic infection. Although apparently correlated, other associated factors were not statistically linked to poor treatment outcomes.

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Conflict of Interests
The authors have no conflict of interests to declare.

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