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Original article

# Infected primary knee arthroplasty: Risk factors for surgical treatment failure☆

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ABSTRACT

*Objective:* To present epidemiological data and risk factors associated with surgical outcomes favorable or unfavorable for the treatment of infection in infected total knee arthroplasty.

*Methods:* We reviewed medical records of 48 patients who underwent treatment of primary total knee arthroplasty for infection between January 1994 and December 2008, in the Orthopedics and Traumatology Department of the Santa Casa de Misericórdia de São Paulo. The variables associated with favorable outcome of surgical treatment (debridement and retention or exchange arthroplasty in two days) or unfavorable (arthrodesis or death) infection.

*Results:* A total of 39 cases of infection after primary total knee arthroplasty, 22 progressed to 17 for a favorable outcome and unfavorable outcome. Early infections (OR: 14.0, 95% CI 1.5–133.2, $p = 0.016$) and diabetes (OR: 11.3, 95% CI 1.4–89.3, $p = 0.032$) were associated with arthrodesis joint and death respectively.

*Conclusion:* Patients with early infection had a higher risk of developing surgical procedure with unfavorable outcome (arthrodesis) and diabetics had higher odds of death after infection of primary knee arthroplasties.



☆ Study conducted at the Department of Orthopedics and Traumatology, School of Medical Sciences, Santa Casa de São Paulo, Fernandinho Simonsen Wing, São Paulo, SP, Brazil. Director: Prof. Dr. Osmar Avanzi.

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## Artroplastia primária de joelho infectada: fatores de risco para falha na terapia cirúrgica

*Palavras-chave:*
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RESUMO

*Objetivo:* Apresentar dados epidemiológicos e os fatores de risco associados ao desfecho cirúrgico favorável ou desfavorável para o tratamento da infecção na artroplastia total de joelho infectada.

*Metódos:* Foram revisados 48 prontuários de pacientes submetidos ao tratamento da artroplastia total primária de joelho por infecção entre janeiro de 1994 e dezembro de 2008 no Serviço de Ortopedia e Traumatologia da Santa Casa de Misericórdia de São Paulo. Foram analisadas as variáveis associadas ao desfecho do tratamento cirúrgico favorável (desbridamento e retenção da artroplastia ou troca em dois tempos) ou desfavorável (artrodeses ou óbito) da infecção.

*Resultados:* Em 39 casos de infecção pós-artroplastia total primária no joelho, 22 evoluíram para desfecho favorável e 17 para desfecho desfavorável. Infecções precoces (RC: 14,0, IC95% 1,5–133,2, p = 0,016) e diabetes (RC: 11,3, IC95% 1,4–89,3, p = 0,032) foram associadas a artrodese da articulação e ao óbito, respectivamente.

*Conclusão:* Pacientes com infecção precoce apresentaram maior risco de evoluir para procedimento cirúrgico com desfecho não favorável (artrodese) e os diabéticos apresentaram maior chance de óbito após infecção de artroplastias primárias no joelho.



## Introduction

Osteoarthrosis is the most prevalent joint disease among elderly adults and it occurs because of the joint cartilage degeneration process. Knee arthroplasty is a surgical technique for treating advanced osteoarthrosis and is being increasingly used because of its good results regarding pain relief and reestablishment of function. Like all surgical procedures, total knee arthroplasty (TKA) is subject to complications over the short or long term, including the following: systemic and thromboembolic phenomena; complications that affect the patellofemoral joint; neurovascular lesions; periprosthetic fractures; loosening of the implanted components; and infection.[1]

Among all the complications, post-arthroplasty infection is one of the most severe and feared types and its incidence may range from 0.5 to 23%.[2,3] Post-arthroplasty knee infections have an economic impact greater than 300 million dollars per year in the countries of North America.[4]

For treatment of infected TKA to be successful, early diagnosis is fundamental, with immediate application of therapeutic measures. Appropriate physical examination, imaging examinations, laboratory tests to investigate inflammatory activity and puncturing of the affected knee may assist greatly in defining the best management.[4]

Regarding the treatment for the infection, several types of surgical procedure have been described, including the following: surgical cleaning with retention of the implant; revision in a one-stage procedure, consisting of removal of the implant, rigorous surgical cleaning and placement of a new prosthesis; revision in two stages, in which implanting the new prosthesis is postponed until a time that some authors consider to be safer; and salvage procedures such as arthrodesis and amputation, in cases of lack of success in previous attempts.[5] All these procedures should be accompanied by appropriate antibiotic therapy according to the pathogens identified as responsible for the infection.[6]

The gold standard for treating cases of infected TKA when implant removal becomes necessary is two-stage revision. In this, intravenous antibiotics are administered for six weeks after debridement and then filling the joint cavity with a spacer comprising orthopedic cement with added antibiotic.[7] The aims in applying the spacer are to maintain the joint distances, occupy the empty spaces between the structures and release high levels of antibiotic at this site.[8] The second stage is performed taking into consideration the possibility of curing the infection,[7] which is confirmed through clinical reassessment and producing a hemogram comprising a leukocyte count and inflammatory marker tests such as the erythrocyte sedimentation rate and C-reactive protein level, and joint puncture in order to culture the synovial fluid.[5] When the results from the examinations are within the range of normality and the cultures are negative, the patient then undergoes the revision, which consists removal of the spacer and placement of a new joint implant that is fixed using cement with added antibiotic.[5,7]

Even though this is a catastrophic complication for TKA patients, with high costs for the healthcare system, few studies have evaluated the factors associated with failure of the surgical methods that are used for curing infected knee arthroplasty cases.[9]

The aim of this study was to make a descriptive analysis of infected TKA cases and the possible risk factors associated with unfavorable outcomes following surgical therapy for the infection.

## Methodology

This was a retrospective case–control study conducted by the Knee Surgery Group of the Department of Orthopedics and Traumatology, Santa Casa de Misericórdia de São Paulo. The population for this study consisted of all the individuals who underwent primary TKA between January 1994 and December 2008, who were identified by means of the database of the institution's Knee Group. Among these, only the patients who presented signs and symptoms of infection subsequent to primary TKA were analyzed through reviewing the medical records. This study was approved by the institution's Research Ethics Committee.

Infections in revision knee arthroplasty procedures and infections confirmed by means of a swab from secretions from the operative wound and/or cases for which insufficient information was available in the medical records were excluded.

The diagnostic criteria for infection associated with arthroplasty were established in accordance with a previously published study.[10] The microbiological confirmation of the infection was done by means of culturing two or more tissue samples from the periprosthetic region, and from bone tissue and identification of the pathogen in the synovial fluid, along with the histopathological description.[11]

All the patients underwent arthrotomy, implant removal, placement of a cemented spacer (PMMA) incorporating vancomycin, provisional immobilization using a splint and use of an orthosis or external fixation, given the great instability of the region. The stabilization method was selected by the same surgeon, according to the stability that had been acquired through placement of the spacer.

Among the variables studied, parameters relating to the patients were evaluated, such as: sex, age, comorbidities (obesity, HIV, previous use of corticoids, diabetes mellitus, arterial hypertension, rheumatoid arthritis and smoking) and the diagnosis that indicated the need for TKA. In relation to the infection, the following data were gathered: the time that elapsed between the surgery and the diagnosis of infection (up to three months after the surgery was considered to be early infection, from three to 24 months was considered to be intermediate infection and 24 months was considered to be late infection)[12] and the bacteria that were isolated from the cultures, which were differentiated between polymicrobial infection (two or more pathogens identified in cultures) and monobacterial infection. The surgical therapy was characterized as revision arthroplasty (surgical debridement with retention of the prosthesis and two-stage revision of an infected prosthesis) or salvage procedures (arthrodesis or amputation).

## Statistical analysis

The descriptive analysis on all the characteristics studied was done using percentages for the qualitative variables and means and standard deviations for the quantitative variables. To analyze the associations between the risk factors and the success of the surgical therapy, we characterized the outcome variable as functional surgical treatment (F) when the cure for the infection was associated with debridement and retention of the prosthesis, or with conventional revision arthroplasty or use of an unconventional endoprosthesis; or as nonfunctional surgical treatment (NF) when the cure for the infection was associated with joint arthrodesis or death associated with the infection. In addition, we analyzed the risk factors associated with infection-related death. For bivariate analyses, Fisher's exact test was used, with the statistical significance level of $p < 0.05$ and a 95% confidence interval. All the analyses were done using the R statistical software, version 2.15.0.[1]

## Results

Out of the 592 patients who underwent primary TKA in the Department of Orthopedics, Santa Casa de Misericórdia de São Paulo, 38 (6.42%) evolved with infection. In addition, ten patients who were included in the sample came from other medical institutions and were referred for treatment at Santa Casa de Misericórdia de São Paulo. Thus, the total sample evaluated in this study was 48 cases of infected TKA. Nine patients (18.75%) were excluded from the analysis because of difficulty in identifying the variables in the medical files.

Among the 39 patients studied, 34 (87.18%) were female and five (12.82%) were male. The age range was from 41 to 89 years, with a mean of 69.7 years (SD ± 10.0 years). The mean length of time between the surgery and the diagnosing of infection was 70.4 weeks (SD ± 15.3). The right knee was affected in 20 patients (51.28%) and the left knee in 19 (48.72%).

The disease that led to the indication of arthroplasty was primary knee arthrosis in 29 patients (74.35%) and the cases of secondary knee arthrosis were consequent to the following: rheumatoid arthritis in two (5.12%), aseptic osteonecrosis of the femur due to corticoid use in two (5.12%), sequelae of septic arthritis in one (2.56%), synovial chondromatosis in one (2.56%), ligament injury in one (2.56%) and post-fracture sequelae in the knee region (including the distal femur and proximal tibia, which affect the joint area) in three (7.68%).

The infectious agents identified were: *Staphylococcus aureus* (31.2%); *Pseudomonas aeruginosa* (22.9%), coagulase-negative *Staphylococcus* (14.5%), *Enterococcus* sp (2.1%), *Enterobacter* (10.4%), *Streptococcus pyogenes* (8.3%), *Escherichia coli* (4.1%), *Proteus mirabilis* (2.1%), *Stenotrophomonas maltophilia* (2.1%) and *Corynebacterium* sp (2.1%) (Table 1). Seven infections were polymicrobial (17.94%) and 32 were monomicrobial (82.06%).

Regarding the presence of comorbidities, 31 patients (79.48%) presented systemic arterial hypertension and nine (23.07%) presented diabetes (types I or II). Diabetes and arterial hypertension occurred in association in eight patients (20.51%); two (5.12%) said that they were smokers; and two (5.12%) presented rheumatoid arthritis. Five patients (12.82%) did not have any comorbidities (Table 2).

According to the time that had elapsed from the surgery to the appearance of signs and symptoms of infection, 19 patients presented early infection (48.72%), eight had intermediate infection (20.52%) and 12 had late infection (30.76%).

[1] www.r-project.org.

**Table 1 – Pathogens identified in intraoperative issue cultures.**

| Types of cultures identified | N | % |
|---|---|---|
| *Staphylococcus aureus* | 15 | 31.25 |
| *Pseudomonas aeruginosa* | 11 | 22.92 |
| *Coagulase-negative Staphylococcus* | 7 | 14.58 |
| *Enterobacter* sp. | 5 | 10.41 |
| *Streptococcus pyogenes* | 4 | 8.33 |
| *Escherichia coli* | 2 | 4.16 |
| *Corynebacterium* sp. | 1 | 2.1 |
| *Stenotrophomonas maltophilia* | 1 | 2.1 |
| *Enterococcus* sp. | 1 | 2.1 |
| *Proteus mirabilis* | 1 | 2.1 |
| Total | 48 | 100.0 |

In relation to therapy for the infected arthroplasty cases, a revision prosthesis implanted in two stages was used in 20 patients (51.3%), a nonconventional endoprosthesis in one (2.6%), arthrodesis in 12 (30.7%) and chronic suppression antibiotic therapy in one (2.6%). Infection-associated death occurred in the cases of five patients (12.8%).

In relation to the analysis on risk factors associated with the therapeutic outcome, i.e. failure (NF) or success (F) of the surgical procedure associated with the cure for the infection in the primary TKA, we observed that variables such as age, sex, presence of primary or secondary arthrosis, identification of bacteria in cultures, monomicrobial or polymicrobial infections, presence or absence of *Staphylococcus aureus*, identification of pathogens in more than one tissue sample and presence of comorbidities did not demonstrate any statistically significant association with the outcomes described. However, in the cases of infection diagnosed up to three months after the surgery (early period), there was a statistically significant association with nonfunctional surgical treatment (NF) (OR: 14.0; 95% CI: 1.5–133.2; $p = 0.016$) (Table 3).

Analysis on the variables associated with death secondary to infection showed that only the patients with diabetes mellitus had a statistically significant association with death (OR: 11.3; 95% CI: 1.4–89.3; $p = 0.032$).

**Table 2 – Distribution of types of comorbidities presented by patients (some of them presented more than one type of comorbidity).**

| Types of comorbidity | N | % |
|---|---|---|
| Arterial hypertension | 31 | 54.4 |
| Diabetes | 9 | 15.8 |
| Rheumatoid arthritis | 2 | 3.5 |
| Smoking | 2 | 3.5 |
| Stroke | 1 | 1.8 |
| Arrhythmia | 1 | 1.8 |
| Corticoid use | 1 | 1.8 |
| Alcohol abuse | 1 | 1.8 |
| Liver disease | 1 | 1.8 |
| Heart failure | 1 | 1.8 |
| Obesity | 1 | 1.8 |
| Liver transplantation | 1 | 1.8 |
| Total | 55 | 100.0 |

## Discussion

It is now known that the number of total arthroplasty procedures performed has been increasing rapidly year by year. It has been estimated that between 2005 and 2030, the number of TKA procedures performed in the United States is expected to increase by up to 673% and reach the level of 3.48 million procedures per year.[6,13] Improvement of the operative techniques and asepsis procedures, and use of preoperative antibiotics, has reduced the risk of infection in primary prostheses.[14,15] However, even with these changes, the increase in the number of procedures has generated ever-greater numbers of cases of infection that require surgical treatment.[15] The infection rates in previous studies ranged from 1% to 5% for infections in primary arthroplasty cases.[16] At Santa Casa de Misericórdia de São Paulo, which is teaching hospital that attends patients within the Brazilian National Health System (SUS), the infection rate after primary knee arthroplasty was assessed as 6.4% over the period from 1994 to 2008. This figure probably reflects surgical treatments for patients with comorbidities such as diabetes mellitus, infections of greater severity (such as those that occur during the early period, i.e. up to three months after the surgery) and polymicrobial infection caused by pathogens presenting greater bacterial resistance. Ong et al.[17] evaluated the risk factors for infection in a cohort consisting of a large number of individuals who underwent primary hip arthroplasty and concluded that in operations performed in medical institutions with public attendance (*Medicare*), presence of comorbidities, male sex and prolonged duration of surgery influenced the infection rates.

Among the patients with a diagnosis of early infection, it was observed that the risk of a nonfunctional surgical outcome from treating infections was 14 times greater than in the cases of intermediate and late infection. The diabetics presented a higher risk of death, possibly associated with the complexity and extent of the infection. Laffer et al.[18] demonstrated that patients with infected knee arthroplasty diagnosed during the intermediate phase presented a higher rate of unfavorable outcomes, probably because of late diagnosis of the infection.

Although without statistical significance, possibly related to the small number of infected individuals in the final sample, the patients of more advanced age and male sex with diabetes presented greater risk of nonfunctional evolution in the surgical treatment. Infections caused by *Staphylococcus aureus* in individuals with secondary arthrosis presented greater risk of death. Galat et al.[9] analyzed the risk factors for early complications of the operative wound in more than 17,000 individuals who underwent primary TKA and found that the presence of diabetes mellitus had a statistically significant association with the risk of infection. Infections in knee arthroplasty cases caused by *S. aureus*, and particularly oxacillin-resistant *S. aureus*, has already been correlated with unfavorable evolution in other published papers.[19]

The mean age of the patients evaluated was 69.4 years and among those of advanced age (over 80 years), there was a nonsignificant association with nonfunctional evolution from surgical therapy, possibly related to the small sample size (odds ratio = 2.2). In a retrospective cohort of infected arthroplasty cases that were treated with debridement and

**Table 3 – Risk factors associated with therapeutic failure or success in treating infected total knee arthroplasty cases.**

| Characteristics | Result | | Total | | *p*-Value[a] | Odds ratio | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Therapeutic success N = 22 (%) | Therapeutic failure N = 17 (%) | N = 39 | (%) | | Estimate | 95% CI[c] | | |
| *Age* | | | | | | | | | |
| 41–59 years | 3 (60.0) | 2 (40.00) | 5 | 12.8 | 0.927 | (ref)[b] | | | |
| 60–69 years | 7 (58.33) | 5 (41.67) | 12 | 30.8 | | 1.1 | 0.1 | – | 9 |
| 70–79 years | 10 (58.82) | 7 (41.18) | 17 | 43.6 | | 1 | 0.1 | – | 8 |
| 80–89 years | 2 (40.0) | 3 (60.00) | 5 | 12.8 | | 2.2 | 0.2 | – | 28.3 |
| *Sex* | | | | | | | | | |
| Female | 20 (60.60) | 13 (39.40) | 33 | 84.6 | 0.374 | (ref)[b] | | | |
| Male | 2 (33.33) | 4 (66.67) | 6 | 15.4 | | 3.1 | 0.5 | – | 19.3 |
| *Diagnosis* | | | | | | | | | |
| Primary | 15 (51.72) | 14 (48.28) | 29 | 74.4 | 0.464 | (ref)[b] | | | |
| Secondary | 7 (70.0) | 3 (30.0) | 10 | 25.6 | | 0.5 | 0.1 | – | 2.1 |
| *Time* | | | | | | | | | |
| Early | 8 (36.36) | 14 (63.64) | 22 | 56.4 | 0.016* | 14 | 1.5 | – | 133.2 |
| Intermediate | 8 (88.89) | 1 (11.11) | 9 | 23.1 | | (ref)[b] | | | |
| Late | 6 (75.00) | 2 (25.00) | 8 | 20.5 | | 2.7 | 0.2 | – | 36.8 |
| *Number of comorbidities* | | | | | | | | | |
| 0 | 3 (50.00) | 3 (50.00) | 6 | 15.4 | 0.738 | (ref)[b] | | | |
| 1 | 14 (60.87) | 9 (39.13) | 23 | 59 | | 0.6 | 0.1 | – | 3.9 |
| 2 or more | 5 (50.00) | 5 (50.00) | 10 | 25.6 | | 1 | 0.1 | – | 7.6 |
| *Hypertension* | | | | | | | | | |
| No | 5 (62.5) | 3 (37.5) | 8 | 20.5 | 1 | (ref)[b] | | | |
| Yes | 17 (54.83) | 14 (45.17) | 31 | 79.5 | | 1.4 | 0.3 | – | 6.8 |
| *Diabetic* | | | | | | | | | |
| No | 20 (62.5) | 12 (37.5) | 32 | 82.1 | 0.206 | (ref)[b] | | | |
| Yes | 2 (28.57) | 5 (71.43) | 7 | 18 | | 4.2 | 0.7 | – | 24.9 |
| Total | 22 (56.41) | 17 (43.59) | 39 | 100 | | | | | |

[a] Result from Fisher's exact test.
[b] Reference group.
[c] 95% confidence interval.
* 5% significance level (*p*-value $p < 0.05$).

maintenance of the prosthesis, the mean age was also high (74 years).[20]

Out of the 39 patients evaluated in our study, 56.4% presented early infection. Intermediate and late infections occurred in 23.1% and 20.5%, respectively. Early infections generally result from perioperative contamination caused by pathogenic agents such as *Staphylococcus aureus* or Gram-negative bacilli, which produce acute manifestations such as local pain, erythema, edema and heat in the operative wound, infected hematomas and fever. Late infections may begin with symptoms of sepsis and generally result from hematogenic dissemination of distant foci.[6,12,21,22]

*Staphylococcus* sp. was identified in 45% of the cases, and *Staphylococcus aureus* in 32%. Byren et al.[19] evaluated infections subsequent to arthroplasty procedures and found *Staphylococcus aureus* in 42% of the cases. Marculescu et al.[20] diagnosed an infection rate due to *Staphylococcus aureus* of 32%, i.e. a figure similar to what we found.

In our sample, 12.8% evolved to death, which was a high number in comparison with Carvalho Junior et al.,[23] who found a death rate of 2.5% out of 120 primary knee arthroplasty cases. However, Morrey et al.[24] found a death rate of 7% out of 501 unilateral knee arthroplasty cases.

Among our patients, 37% evolved to salvage surgical procedures (nonfunctional), which was a higher number with this outcome than found by D'Elia et al.,[25] who found that only 6.9% of their patients showed this, between 2003 and 2004. It is important to emphasize that revision arthroplasty to treat infections was not so commonly performed in our institution in the 1990s, which resulted in a larger number of arthrodesis procedures in the past. From 1994 to 2001, 20 cases were evaluated due to infection. Of these, eight (40%) underwent arthrodesis. On the other hand, from 2002 to 2008, there were 19 cases, of which four (21%) underwent arthrodesis.

## Conclusion

Patients with early infection presented greater risk of evolving toward surgical procedures with nonfunctional outcomes (arthrodesis) and diabetics presented a greater chance of death after infection of primary TKA.

## Conflicts of interest

The authors declare that there were no conflicts of interest.

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