



## Original article

## Haematogenous prosthetic knee infections: Prospective cohort study of 58 patients



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## ABSTRACT

**Background:** Prosthetic joint infection (PJI) is a rare (incidence, 0.15% to 0.9%) but serious complication of knee arthroplasty. Haematogenous PJI of the knee (KhPJI) which accounts for 10% of cases, has been less studied than PJI due to other mechanisms. The primary objective of this study in patients with KhPJI of the knee was to determine the 2-year infection eradication failure rate after either exchange arthroplasty or arthrotomy/synovectomy/irrigation (ASI), combined with prolonged peri-operative antibiotic therapy, at a referral centre for complex osteo-articular infections.

**Hypothesis:** ASI within 2 weeks after symptom onset and one-stage exchange arthroplasty produce similar 2-year success rates in patients with KhPJI of the knee.

**Material and Methods:** A prospective observational cohort study was performed in patients managed for PJI of the knee between 2003 and 2015. The primary outcome measure was the occurrence of a septic event or of KhPJI -related death during a minimum follow-up of 2 years.

**Results:** Of 265 patients with PJI after total knee arthroplasty, 58 (22.1%) had KhPJI with onset more than 3 months after the last arthroplasty procedure and were included in the study. Among them, one-third had immune deficiencies. The most common causative organisms were streptococci ( $n = 25$ , 43%) and *Staphylococcus aureus* ( $n = 20$ , 34%). The primary focus of infection was identified in only 64% of patients and was most often cutaneous ( $n = 19$ , 33%) or dental ( $n = 11$ , 19%). A septic event or KhPJI-related death occurred in 5/34 (15%) patients after one-stage exchange arthroplasty and 6/19 (32%) patients after ASI within 15 days after symptom onset ( $p = 0.03$ ). Patient characteristics, type of prosthesis, and causative organism were not significantly associated with failure to eradicate the infection.

**Conclusion:** ASI carried a high failure rate despite being performed within 15 days after symptom onset. One-stage exchange arthroplasty seems to be the best surgical option, particularly as the exact time of symptom onset may be difficult to determine. Identifying and eradicating the primary focus of infection is crucial.

**Level of evidence:** II, low-powered prospective cohort study.

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## 1. Introduction

Prosthetic joint infection (PJI) is a serious complication of knee arthroplasty that continues to occur despite improvements in surgical techniques and prophylactic measures. The incidence of knee PJI ranges from 0.15% to 0.90% [1–5]. PJI is a major source of comorbidity exacerbations, which requires multiple admissions, thereby substantially increasing healthcare costs [6–13]. Haematogenous

PJI at the knee, which accounts for 10% of all PJIs [14,15], has received less research attention than other mechanisms of infection.

Haematogenous infections often present as the abrupt onset of prominent manifestations after a symptom-free period. The symptoms of haematogenous PJI may include joint pain, local evidence of inflammation, a fever, and marked elevation of blood markers of inflammation. The causative organism spreads from an extra-articular infection to the joint via the bloodstream. The exact times of symptom onset and implant contamination may be difficult to determine. This presentation contrasts with the more insidious and at times smouldering manifestations of delayed PJI due to intra-

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operative joint contamination, whose time of occurrence can be determined with accuracy as the time of the last surgical procedure on the implant.

The definition of haematogenous infection has changed considerably since the first publications by Schmalzried et al. [16] and Tsukayama et al. [17]. Crockarell et al. recently suggested defining haematogenous PJI at the hip as the acute onset of symptoms more than 1 month after the arthroplasty procedure, after a period of good prosthesis function [18]. Nevertheless, the haematogenous origin of the PJI may be difficult to prove as the exact time of symptom onset may be unclear, the primary focus of infection challenging to identify, and blood cultures inconsistently positive. The medical history and physical examination can then provide valuable clues pointing to an overlooked extra-articular infection, such as a minimally symptomatic gastrointestinal lesion, dental procedures in the more or less recent past, or a skin lesion, which may have led to bacteraemia. The primary focus may be resolved at the time of PJI symptom onset or management, making its identification particularly difficult.

The treatment of chronic PJI due to intra-operative contamination requires complete exchange arthroplasty, in one-stage (1XA) or two stages (2XA), combined with prolonged antibiotic therapy [19]. In contrast, in acute PJI, given the shorter duration of the infection, conservative treatment by arthrotomy/synovectomy/irrigation and exchange of mobile components may be appropriate [20–23] provided it is performed early, before implant colonisation and protective biofilm formation by the organism. Combining this conservative strategy with prolonged antibiotic therapy holds appeal as a means of optimising functional outcomes by decreasing the aggressiveness of the procedure compared to 1XA, which can also be used in this situation [24,25].

Conservative surgery without exchange arthroplasty as a treatment for Haematogenous PJI of the knee (KhPJI) has been evaluated only in small sample sizes [26]. Furthermore, patients with acute post-operative contamination and those with haematogenous contamination were generally pooled, despite the difference in the mechanism of infection. No risk factors for failure of conservative surgical management have been identified [13,27].

The primary objective of this study was to determine the 2-year infection eradication failure rate of KhPJI treated with either 1XA or arthrotomy/synovectomy/irrigation (ASI), combined with peri-operative prolonged antibiotic therapy, at a referral centre for complex osteo-articular infections. Our working hypothesis was that ASI within 15 days after symptom onset and 1XA produce similar 2-year success rates in patients with KhPJI.

## 2. Material and Methods

### 2.1. Study design and patients

The protocol for this single-centre observational prospective cohort study was approved by our institutional review board. The cohort consisted of patients managed at a referral centre for complex osteo-articular infections between 2003 and 2015.

The inclusion criteria were: age above 18 years, informed consent to study participation, microbiologically documented PJI of the knee meeting Parvizi's criteria [28], eligibility to curative surgical treatment and haematogenous joint contamination established by medical chart review by two experts based on the following criteria: abrupt onset of pain with or without local inflammation after a period of satisfactory prosthesis function and/or fever with chills, symptom onset at least 3 months after the last prosthetic surgical procedure and recovery of the same organism within the joint and an extra-articular focus of infection if identified or strongly suspected. The 3-month time interval was chosen to rule

out intra-operative joint contamination because the time to recovery is longer after knee compared to hip arthroplasty. Thus, 1 month after knee arthroplasty, many patients still experience pain and functional limitations, even in the absence of evidence suggesting active PJI. Patients with mycobacterial PJIs were not included.

### 2.2. Endpoints

The primary endpoint was the occurrence of a septic event (relapse or new infection) or KhPJI-related death within 2 years after initial KhPJI treatment. The secondary objectives of the study were to assess the epidemiological and bacteriological characteristics of KhPJI.

### 2.3. Data collection and definitions

Immune deficiency was defined as any of the following: immunosuppressive therapy, history of organ transplantation, active malignancy within the past 5 years, and diabetes. Symptom duration was measured from the onset of the first symptom of KhPJI (fever, pain, wound dehiscence, or local inflammation) and the time of curative surgery for KhPJI. Failure to eradicate the infection was defined as either a further septic event (relapse of the KhPJI, due to the same organism; or new KhPJI, due to a different organism) or death directly ascribable to the KhPJI or its treatment, within the first 2 years after curative KhPJI surgery.

In patients with more than one joint prosthesis, the number of prosthetic joints was recorded. The types of knee prostheses included standard total posterior-stabilised or ultra-congruent implants, semi-constrained or hinged implants, unicompartmental implants and massive implants.

The causative organism(s) were recovered in blood cultures and/or joint aspirates obtained pre-operatively or in multiple specimens collected intra-operatively. At the time of the diagnosis of KhPJI, the patients were routinely investigated for an extra-articular lead point (e.g., in the skin, oral cavity, gastrointestinal tract, urinary tract, or other implanted foreign material).

### 2.4. Treatments

When performed within 15 days after symptom onset, curative surgical treatment consisted of ASI with exchange of the polyethylene implant (when the necessary material was available) but retention of the prosthesis. Otherwise, 1XA or 2XA with synovectomy was performed.

Antibiotics were given for 6 weeks in patients with acute infection and 12 weeks in those with more long-standing infection. The antibiotics were routinely selected during a multidisciplinary discussion. Rifampicin was consistently among the antibiotics used in patients with KhPJI due to a susceptible *Staphylococcus*, in the absence of contra-indications. Amoxicillin was used alone in patients with streptococcal or enterococcal infections. Infections due to enterobacteriaceae were treated by beta-lactams followed by an oral fluoroquinolone when the organism was susceptible [29,30].

### 2.5. Statistical analysis

The statistical analyses were performed using R version 3.4.1 (<https://www.r-project.org/>). Qualitative variables were described as number (%) and quantitative variables as median (interquartile range). Recurrence-free survival and KhPJI-related mortality were assessed using the Kaplan–Meier method and compared by applying the log-rank test. Univariate analyses were performed using

the chi-square or Fisher's exact test and Student's *t* test. Logistic regression models were built for the multivariate analyses.

### 3. Results

Of 265 patients with PJI after TKA managed at our centre during the study period, 58 (22%) met the study inclusion criteria (Appendix A). Among them, 34 were managed by 1XA, 21 by ASI, and 3 by two-stage XA (2XA). Median follow-up was 39.7 months (range, 8.1–128.1 months). Four patients were lost to follow-up within the first 2 years. Appendix A reports the main features of the study patients.

Median time to symptom onset after the last clean surgical procedure was 33 months (range, 3–1334). Median symptom duration (from the first evidence of infection to surgical revision) was 20 (2–371) days overall, 64 days in the 1XA group, and 5 days in the ASI group. The blood cultures were positive in 16 (28%) patients on the day of admission to our centre. The most commonly recovered organisms were streptococci ( $n=25$ , 43%) and *Staphylococcus aureus* ( $n=20$ , 34%). The source of infection was cutaneous or dental in most patients (Appendix A). In over one-third of patients, no definitive proof of an extra-articular lead point was found, but the organisms recovered were consistent with an extra-articular infection.

A KhPJI-related event occurred within 2 years in 15 (26%) patients, 8 in the ASI group and 7 in the XA group. Of these 15 patients, 6 (6/58, 10%) experienced a relapse of the same infection at a median of 15 (3–369) days after surgery and 7 (12%) had a new infection in the same joint at a median of 12 (2–23.3) months after surgery. The remaining 2 (2/58, 3%) patients died of treatment-related events: 1 experienced a fatal pulmonary embolus 1 month after surgery and the other died of cardiorespiratory arrest on the day after surgery.

Of the 21 patients in the ASI group, 8 (38%) experienced KhPJI-related events, including 6 with relapses and 2 with new infections. Symptom duration was 15 days or less in 19 of these patients, with a median symptom duration of 8 (2–15) days. The remaining 2 patients had surgery 19 and 25 days, respectively, after symptom onset, and both experienced treatment failure. Of the 34 patients managed by 1XA, 5 (15%) had further KhPJI-related events (new infections in 3 and KhPJI-related death in 2). Of the 3 patients managed by 2XA, 2 (66%) experienced treatment failure.

Of the 24 patients who had surgery within 15 days after symptom onset, 19 were managed by ASI, including 6 (32%) who experienced treatment failure; 3 underwent 1XA, including 1 (33%) with treatment failure; and 2 had 2XA, including 1 with treatment failure. Of the 12 patients who underwent ASI within 8 days after symptom onset, 4 (33%) experienced treatment failure.

Potential risk factors tested by univariate and multivariate analysis included demographic characteristics, immune deficiency, body mass index, type of knee prosthesis, number of prostheses, and microbiological documentation. Thus, no factors other than the surgical technique were found to be associated with treatment failure (Appendix A).

The proportion of patients with no KhPJI-related events within the first 2 years was 85.3% in the 1XA group and 68.4% in the group managed by ASI within 15 days after symptom onset ( $p=0.03$ ) (Appendix A). Two-year survival in these two groups, regardless of time from symptom onset to surgery, was 85.3% and 61.9%, respectively ( $p=0.01$ ). At last follow-up, 8 patients had experienced new infections, with onset after the first 2 years. No patient experienced a relapse after the first 2 years (Appendix A).

### 4. Discussion

This study reports on 58 cases of KhPJI seen among 265 cases of knee PJI and managed at our centre between 2003 and 2015. To our knowledge, this is the largest cohort of KhPJI of the knee described to date.

Within 2 years after curative treatment, an infectious event occurred in 15 (26%) patients (6 with relapses, 7 with new infections, and 2 with KhPJI-related death). Treatment consisted in ASI, 1XA, or 2XA combined with antibiotic therapy for at least 6 weeks. The success rate was significantly higher with 1XA than with ASI.

The causative bacteria were similar to those reported previously, with a predominance of *S. aureus* and streptococci, which more often cause haematogenous than intra-operative contamination [31]. Nearly 30% of our patients had immune deficiencies, which probably increased their susceptibility to infection. This finding emphasises the need to raise awareness among patients and physicians about the importance of correcting modifiable risk factors for infection and promptly treating extra-articular infections, notably of the skin and teeth, which are the most common lead points [32].

No risk factors for failure other than the surgical technique were identified. Thus, patient-related factors, type of knee prosthesis, number of prosthetic joints, and type of causative organism were not associated with the occurrence of infectious events after curative treatment.

ASI, with polyethylene insert exchange if the required material is available, was recommended by learned societies in the US in 2013 [33] and the French High Authority for Health in 2014 [34] for patients with early PJI of the knee due to intra-operative contamination. Most studies showed good outcomes after the use of method, with success rates ranging from 70% to 88% [35–38]. However, these good outcomes are not replicated in KhPJI, even when treated early. Thus, our study does not support ASI for the treatment of KhPJI: failures rates were 38% for ASI overall and 33% for ASI within the first 15 days after symptom onset, compared to 15% in the 34 patients who underwent 1XA ( $p=0.01$ ). Marculescu et al. advocated ASI in patients with symptom onset within the past 8 days [39]. However, in the 12 patients treated within 8 days in our study, ASI did not produce higher success rates than in the overall ASI group. These globally mediocre outcomes of ASI are in agreement with data obtained by Fink et al. [30]: with ASI within 21 days after symptom onset, the success rate was 82% in early PJI due to intra-operative contamination but only 57% in KhPJI. Outcomes were better when ASI was performed within 2 days after symptom onset [30].

Of the 19 patients managed with ASI in our study, 2 were performed more than 15 days after symptom onset, namely, after 19 days in a patient in whom 1XA was deemed inadvisable due to a high operative risk and after 21 days in a patient with severe sepsis in whom the goal of ASI was to decrease the bacterial burden before perhaps performing exchange arthroplasty later on. The treatment failed in both patients, but no other options were available.

In previous studies, ASI failure rates in haematogenous PJI of the hip or knee ranged from 23% to 30% [40–45]. One possible explanation to this high failure rate is that the time of infection onset and, therefore, the true duration of the infection, may not be accurately assessable based on the information supplied by the patient. In addition, patients with chronic infection may abruptly experience a symptom exacerbation that mimics an acute infection. The result is an underestimation of the duration of the infection, which is too firmly entrenched to be treatable by ASI. A crucial step is therefore a careful patient interview about the post-operative course after the last prosthetic procedure, the modalities and time of symptom onset, and any evidence of potential lead points (dental, urinary, cutaneous, gastrointestinal, or other). Equally indispensable is a

thorough physical examination, notably of the skin, to determine the type of infection and the best strategy for treating the KhPJI. Any radiographic abnormality of the implant or bone in contact with the implant should suggest chronic infection.

Regarding pathophysiological mechanisms, contamination via the bloodstream may conceivably inoculate intra-osseous sites that are not accessible by irrigation. In contrast, after intra-operative contamination, the bacteria are located within the joint from where they can be removed by synovectomy and irrigation.

Acute haematogenous *S. aureus* infections are generally reported as associated with higher failure rates. In our study, the failure rate in *S. aureus* KhPJI was 38%, compared to 60%–92% in earlier studies [26,27,38,46]. In streptococcal infections managed by ASI, the failure rate was greater than 40% in a study by Lora-Tamayo J et al. [47], compared to 17% (1 of 6 patients) in our work. Another study found no evidence that the nature of the organism influenced the outcomes of ASI [48].

Eradication of the primary focus of infection is pivotal to prevent recurrences. The large number of new infections in our patients may be ascribable to failure to identify, and therefore to eradicate, the lead points in a substantial proportion of patients at the time of KhPJI management.

The main limitation of our study is that the haematogenous mode of contamination was not consistently confirmed by positive blood cultures at the time of the diagnosis. In addition, we extended the time since joint replacement surgery to 3 months to define haematogenous infections, to limit the risk of including patients with early PJI after intra-operative contamination. The most relevant time interval remains controversial [14,16–18,46]. We excluded 5 patients with a strong suspicion of haematogenous infection because symptom onset occurred less than 3 months after the joint replacement procedure.

The proportion of PJIs due to haematogenous contamination may be underestimated. It has been suggested that haematogenous contamination may be the main mechanism responsible for PJI [9,16]. The diagnostic criteria for KhPJI remain controversial. Thus, a positive blood culture clearly constitutes strong support for a diagnosis of KhPJI yet is not included in all definitions of KhPJI [16–18] because the primary focus of infection and bacteraemia usually resolve before the diagnosis of PJI. In our study, only 16 patients had positive blood cultures. Consequently, this parameter was not analysed. Although rarely positive at the time of the diagnosis of KhPJI, a routine blood culture remains recommended.

In conclusion, 1XA may be more appropriate than ASI to eradicate KhPJI. In our study, 1XA was successful in 85% of cases. Although ASI is appealing as a less aggressive procedure than exchange arthroplasty, it should be borne in mind that failure of ASI may adversely affect the chances of successful future exchange arthroplasty, as reported by Sherell et al. [49].

In addition to providing a high success rate, 1XA does not require an accurate estimation of symptom duration, obviates the need for emergent surgery inconsistent with optimal medical preparation and technical conditions, allows time to document the infection by joint aspiration and to identify and treat the primary focus of infection and, in some cases, allows antibiotic therapy initiation before surgery. This KhPJI management strategy requires evaluation in a larger number of patients.

#### Disclosure of interest

The authors declare that they have no competing interest.

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None.

#### Contributions

Thomas Stévignon: collected the study data, drafted and revised the manuscript.

Antoine Mouton: conceived the study, performed surgery on some of the patients, revised the manuscript.

Vanina Meyssonier: conceived the study, contributed to pharmacological patient management, revised the manuscript.

Younes Kerroumi: collected the study data, performed the statistical analysis.

Alexandre Yazigi: performed the statistical analysis.

Thomas Aubert: performed surgery on some of the patients.

Luc Lhotellier: performed surgery on some of the patients.

Vincent Le Strat: performed surgery on some of the patients.

Dorick Passeron: performed surgery on some of the patients.

Wilfrid Graff: performed surgery on some of the patients.

Valérie Zeller: contributed to pharmacological patient management.

Béate Heym: contributed to the bacteriological management.

Simon Marmor: conceived the study, performed surgery on some of the patients, revised the manuscript.

#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.otsr.2019.02.022>.

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