



Case Report

Single-Stage Revision With Fluconazole Monotherapy in Fungal Prosthetic Knee Joint Infections

James C. George, D Ortho, MS (Orthopaedics), Jishar Sainulabdeen, MS (Orthopaedics) *, Samuel Chittaranjan, MS (Orthopaedics), FRCS (Trauma and Orthopaedics), Koshy George, MS (Orthopaedics), Subin Babu, MS (Orthopaedics)

Department of Orthopaedics, Believer's Church Medical College and Hospital, Thiruvalla, Kerala, India

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ABSTRACT

Fungal prosthetic joint infection is rare, and two-stage revision is usually advocated. We present our experience with 2 cases of fungal prosthetic knee joint infection presenting 25 months and 3 years after index surgery. Both patients were managed with single-stage revision arthroplasty and fluconazole monotherapy. They remain asymptomatic with good knee society score after 2 years of follow-up. Preoperative workup of all aseptic loosening cases should include extended culture for fungal elements. Single-stage revision with antifungal therapy for 3 months gives good results in non-immunocompromised patients with good soft-tissue envelope.

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Introduction

Prosthetic joint infection (PJI) is one of the most dreaded and complex complications [1] of total joint arthroplasty and is now the major cause of failure after total knee arthroplasty [2]. Fungal infections are often seen associated with bacterial prosthetic joint infections managed with staged treatment. Primary fungal PJIs are rare and attributed to 1% of all periprosthetic joint infections. These infections pose a challenge to diagnosis and treatment and are frequently complicated by host factors such as presence of systemic illness and immunocompromised state.

There are no established guidelines for treating fungal PJIs. Most authors favor a staged revision arthroplasty with or without cement spacer, for which a recurrence rate of up to 25% has been reported [3–6]. Single-stage exchange knee arthroplasty has been reported by Selmon et al. and Klatte et al. [7,8]. We report 2 cases of fungal prosthetic knee joint infection treated with single-stage exchange arthroplasty. Informed consent was obtained from both the patients for the purpose of publishing the case reports.

Case histories

Case 1

A 65-year-old lady with type 2 diabetes underwent left total knee replacement in 2015. She had persistent minimal pain around the knee since the index surgery. She presented 25 months after surgery with an aggravation of knee pain. Patient had effusion and a painful knee flexion up to 90°, with no fever or sinus communicating with the knee. Total white blood cell (WBC) count was normal, C-reactive protein (CRP) was 13.6, and erythrocyte sedimentation rate (ESR) was 94 (Table 2). Knee radiographs showed loosening in all zones of the tibia and in zone 1–4 of the femur (Fig. 1). The knee was aspirated, and joint fluid was sent for culture (BACTALERT, bioMerieux, Marcy-l'Étoile, France) which remained negative for any organism after 72 hours. The sample was kept for an extended culture which then grew *Candida parapsilosis* after 7 days and was sensitive to fluconazole.

Antifungal monotherapy was initiated with 200 mg of oral fluconazole twice daily for 3 weeks until surgery. Intraoperatively, synovial fluid and 5 tissue samples were sent for culture (BACTALERT and Sabouraud dextrose agar). A thorough debridement was performed removing all suspected infected tissue and cement debris. Revision knee replacement was performed using gentamycin-loaded cement to which 2 gm of vancomycin was added (Fig. 2).

* Corresponding author. Kumbalath House, Thrikkunnapuzha P.O., Alappuzha, Kerala, 690515, India. Tel.: 97450381224.

E-mail address: drjishar.sa@gmail.com

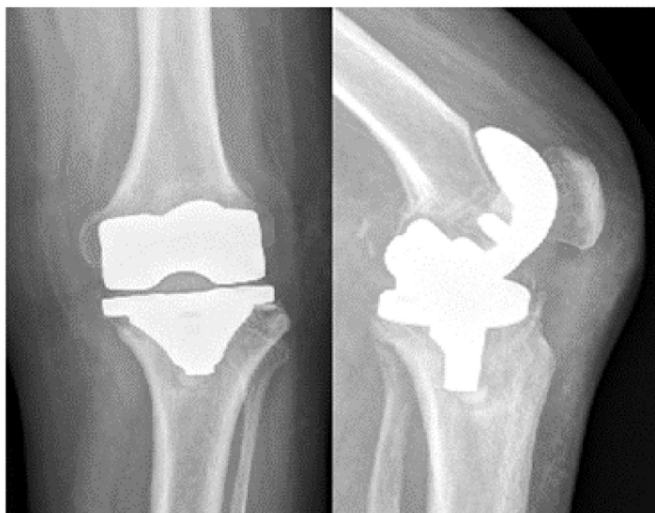


Figure 1. Preoperative radiographs showing tibia and femoral loosening.

Cultures grew *Candida parapsilosis*. Postoperatively, 6 doses of prophylactic intravenous cefazolin were administered. Oral fluconazole, 200 mg twice daily, was continued for 3 months. Patient underwent standard physiotherapy for primary total knee replacement. Wound healed uneventfully by 2 weeks. She was followed up at 6 weeks and 3 months with serial monitoring of CRP. At 3-month follow-up visit, she did not have pain or swelling over the knee, and CRP was normal. Therefore, antifungals were stopped. She continued to remain asymptomatic without any recurrence of infection at 30 months of follow-up. Her Knee Society score [9] at 2 years is shown in Table 1.

Case 2

A 64-year-old lady presented 3 years after total knee arthroplasty with progressive knee pain for 18 months duration. She did not have any medical comorbidities. Clinical examination revealed minimal effusion in the knee with flexion to 70° with pain. CRP and ESR were normal (Table 2). Total WBC count was normal. Plain



Figure 2. Postoperative radiographs showing revision knee system.

Table 1
Knee Society score.

Criteria (maximum score); patient	Expectation (15)	Satisfaction (40)	Function (100)	Symptoms (25)	Objective (75)	Total (255)
Patient 1	11	30	39	16	70	166
Patient 2	13	28	44	19	72	176

radiographs showed a tibial loosening with varus deformity of the component (Fig. 3). Joint aspirate was sent for aerobic culture (BACTALERT) which did not grow any organism.

She was suspected to have aseptic loosening and taken up for revision arthroplasty. Intraoperatively, synovial fluid and 5 tissue samples were sent for culture. Revision surgery after meticulous debridement was completed with azithromycin-loaded cement (Fig. 4). Six doses of prophylactic cefazolin were administered. Both fluid and tissue samples grew nonalbicans *Candida* species sensitive to amphotericin and fluconazole. She was given 3 months of oral fluconazole, 200 mg twice daily. Regular follow-up at 6 weeks and 3 months with serial monitoring of CRP was performed. She has completed 3 years of follow-up without any reinfection and a good Knee Society score [9] (Table 1)

Discussion

Periprosthetic fungal infections are rare, and the diagnosis may be missed during evaluation of a painful prosthetic knee. PJI's pose an enormous economic burden to the patient [10]. Therapeutic and diagnostic guidelines for fungal PJI's have not been clearly established. The International Consensus Group has found some general agreement, but no definitive guidelines or recommendations exist [11,12].

Bacterial PJI's have been treated with single- or two-stage exchange arthroplasties. A recent meta-analysis has shown that one-stage exchange arthroplasty may provide superior outcomes, including lower reinfection rates and superior function in selected patients. The rate of recurrent infection ranged from 0% to 18%, at a minimum 2 years of follow-up [13]. Worst outcomes were noted in the presence of severe immunocompromised state and significant soft-tissue or bony compromise and concurrent acute sepsis [13]. For fungal PJI's, most authors recommend a two-stage revision. The rates of recurrent infection vary widely, and maybe upto 25% [6].

Hwang et al. had 6.6% reinfection rate, and Anagnostakos et al. had 0% reinfection rate [3,4]. Coexisting bacterial infection along with fungal infections were reported in 6 of the 30 knees operated by Hwang et al. [3]. Klatte et al. reported outcomes of single-stage revision for fungal PJI in 10 patients (6 hips and 4 knees) [8]. One reinfection with *Candida parapsilosis* was seen in an immunocompromised patient on chronic steroids, and 3 had bacterial superinfections [3,8]. Among the 4 patients who had single-stage revision total knee replacement, one was immunocompromised,

Table 2
Blood investigations.

	Preoperative			At last follow-up		
	Total WBC count 4800-10800/ μ L	ESR 0-15 mm/HR	CRP <10 mg/L	Total WBC count 4800-10800/ μ L	ESR 0-15 mm/HR	CRP <10 mg/L
Patient 1	4600	94	13.6	-	-	3.1
Patient 2	8600	18	8	-	-	5

CRP, C-reactive protein; WBC, white blood cell count.



Figure 3. Preoperative radiographs showing tibial loosening and varus alignment.

and 2 had sinuses requiring revision surgeries without exchange of implant until complete cure.

In the study by Hwang et al. on two-stage revision, 8 out of 30 patients were immunocompromised [3]. The average age of patients in most studies and meta-analysis is above 60 years [13]. Systemic diseases such as cardiac disease and diabetes are prevalent in more than 50% of the patients, while immunocompromised states due to steroid use, rheumatoid arthritis, renal disease, and malignancies is present in less than 50% [6]. About 13% of patients have no risk factors [6].

Amphotericin B and fluconazole are 2 common antifungals used for *Candida* infections. Amphotericin B is nephrotoxic and can be used for only selected patients. It is not heat stable and may not elude from the bone cement after 48 hours [14,15]. Oral fluconazole is less toxic and has shown good synovial fluid and serum concentrations comparable to amphotericin while treating *Candida*



Figure 4. Postoperative radiographs showing single axis revision knee system addressing the varus malalignment and loosening

infections [16,17]. Similar to bacteria, *Candida* species also produce biofilms impermeable to antifungal agents [18,19].

The patients reported here were not immunocompromised and had a near-normal soft-tissue envelope. Our first patient was treated with antifungals for 3 weeks and then taken for surgery. Contamination with fungal elements was excluded by repeating the culture preoperatively. Our second patient did not show any elevation of CRP, WBC count, or ESR in the preoperative evaluation. A diagnosis of aseptic loosening was favored over periprosthetic joint infection. Extended culture of both BACTALERT and Sabouraud dextrose agar showed nonalbicans *Candida* species. Therefore, extended culture for fungal elements should be considered for preoperative evaluation of all cases of aseptic loosening.

Oral fluconazole has good bioavailability. As per Infectious Diseases Society of America (ISDA) guidelines, *Candida* bone infections require 6–12 months of antifungals, and septic arthritis requires 6 weeks of antifungals [20]. Hwang et al. and Azzam et al. used parenteral and oral antifungals for 6 months, while Klatte et al. for 6 weeks based on CRP values [3,6,8]. The side effects of antifungal agents are well known when given for long duration [21]. Our patients were treated with antifungals for 3 months till CRP was within normal limits. We believe invasive fungal species may have late recurrence and hence would require long-term antifungal therapy. Close follow-up with clinical and inflammatory markers is prudent.

Summary

In conclusion, preoperative workup of all aseptic loosening cases should have extended culture for fungal elements, even in the absence of risk factors. In patients who are not immunocompromised and have a good soft-tissue envelope around the knee, a single-stage exchange arthroplasty can give good functional results. Preoperative oral fluconazole can reduce the fungal load during revision surgery. Prolonged postoperative antifungals should be administered guided by CRP levels. Further experience with single-stage revisions for fungal PJI is required for establishing clear guidelines and treatment protocols.

Conflict of interest

The authors declare there are no conflicts of interest.

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