Fungal Infection in Total Joint Arthroplasty

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Delayed Reimplantation Arthroplasty for Candidal Prosthetic Joint Infection: A Report of 4 Cases and Review of the Literature

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Introduction

Fungal prosthetic joint implants (PJIs) are rare. MacGregor et al. reported the first case of candidal PJI in 1979. During the past 21 years, only 30 cases of PJI due to Candida species have been reported in the medical literature. The percentage of PJIs due to Candida species is unknown, but it is estimated to be 1%.
Risk factors

Risk factors for the development of invasive candidal infections include: immunosuppression, neutropenia, chronic or prolonged use of antibiotics, presence of indwelling intravenous catheters, parenteral hyperalimentation, malnutrition, diabetes mellitus, rheumatoid arthritis, cirrhosis, history of multiple abdominal surgeries, history of renal transplantation, severe burns, and injection drug use.
Despite knowledge regarding these risk factors, approximately one-half of the reported cases of candidal PJI have no identifiable risk factor.
Successful treatment of candidal PJI has been reported, and most often, it has required removal of the joint prosthesis combined with directed antimicrobial therapy. Many investigators have been reluctant to perform delayed reimplantation arthroplasty because of a perceived high risk of relapse of infection.
Definitive information regarding therapy is limited; however, recently published practice guidelines for the treatment of candidal infections advise use of resection arthroplasty with antifungal therapy as the standard therapeutic option and suggest that, after successful therapy, a new prosthesis may be implanted.
**Study design:** A retrospective case series and medical literature review.

**Population:** All patients with a total hip arthroplasty (THA) or total knee arthroplasty (TKA) infections due to *Candida* species (according to a strict case definition) who were treated with delayed reimplantation arthroplasty during the period of 1969-1999.
**Case definitions:** Candidal PJI as "definite" if 2 cultures of either a joint aspiration specimen or a surgical specimen yielded *Candida* species, in conjunction with an appropriate clinical syndrome.
Results

A total of 46 cases of candidal PJI that occurred during the period of 1969-1999.

Of these cases, 30 had been reported elsewhere in the medical literature and 16 were diagnosed at our institution but not previously reported.

THA, TKA, and total shoulder arthroplasty PJI accounted for 21 (45.6%), 23 (50.0%), and 2 (4.3%) of the 46 cases, respectively.
For the whole series of THA and TKA infections, definitive treatment included 25 permanent resection arthroplasties (56.8%), 10 delayed reimplantation arthroplasties (22.7%), 5 debridements with prosthesis retention (11.4%), 2 direct exchanges (4.5%), 1 amputation (2.3%), and 1 case treated with medical therapy alone (2.3%).
There were 6 THA and 4 TKA infections in 5 men and 5 women.
The initial arthroplasty was cemented in 7 cases and uncemented in 1; in 2 cases, information was not available.
Vancomycin-impregnated bone cement was used in 2 of these patients.
The median duration of time from prosthesis implantation to the onset of symptoms was 20.3 months.
Six (60%) of 10 patients had identifiable risk factors for *Candida* infection and/or candidal PJI, with the majority of those patients (5 [83.3%] of 6) having >1 risk factor
Microbiology

No patient had a polymicrobial infection at the time of diagnosis.

In all cases, the intraoperative cultures yielded Candida species.

Six cases (60%) were due to Candida albicans, 3 (30%) were due to Candida parapsilosis, and 1 (10%) was due to Candida tropicalis.
Prior to diagnosis, 9 patients had provided a preoperative aspirate specimen. Aspirate specimens were positive on Gram stain for yeast or fungal elements for only 2 patients (22.2%); however, culture of these specimens was positive for *Candida* species for 8 patients (88.9%).
Surgical therapy:

Resection arthroplasty was the initial intervention for 8 (80%) of 10 patients.

Of the 2 patients for whom resection arthroplasty was not the initial treatment, one had relapse after receiving medical therapy alone, and initial debridement was unsuccessful for the other.

Gross purulence was noted in 6 patients (75%) at the time of surgery.
Of the 4 patients treated, staged irrigation and debridement with removal of all cement and necrotic tissue was performed concurrently with resection arthroplasty.

Three patients underwent irrigation with saline and 1 underwent irrigation with a saline-neomycin solution. No patient underwent irrigation with a solution that contained amphotericin B or fluconazole.

In 1 patient, a polymethylmethacrylate spacer was placed that contained 200 mg of fluconazole.

No other patient received local antifungal therapy in the form of antifungal irrigation or impregnated beads or spacers.
The median duration of time from resection arthroplasty to reimplantation for THAs and TKAs was 8.6 months (range, 2.4-17.7 months) and 2.3 months (range, 0.3-6.0 months), respectively.

Reimplanted prostheses were cemented in all patients for whom this information was available (6 [60%] of 10). Three of the 6 patients received antibiotic-impregnated bone cement (vancomycin for 1 patient and a combination of vancomycin and tobramycin for 2).
No patient received antifungal-impregnated cement at the time of reimplantation.

In the 8 cases for which the results of cultures had been reported at the time of reimplantation, the results of fungal cultures were negative.

After surgery, 1 patient developed serous drainage. An aspiration specimen obtained 1 week earlier yielded negative results on culture, and at the time of reimplantation, the bone and soft tissues did not appear to be infected; however, 3 intraoperative cultures revealed *Staphylococcus epidermidis*.

The patient was treated with cefazolin for 24 days, followed by treatment with orally administered cephradine.
Systemic antifungal therapy was administered to all but 1 patient; 8 patients (80%) received amphotericin B, of whom 3 (37.5%) received amphotericin B alone, 2 (25%) received concurrent 5-fluorocytosine, and 3 (37.5%) received induction amphotericin B, followed by either (1) fluconazole or (2) ketoconazole followed by fluconazole.
The median daily dose of fluconazole was 200 mg and the median duration of therapy was 122 days; this includes data for 1 patient who received maintenance therapy for suppression. One patient received monotherapy with fluconazole (200 mg per day for 6 weeks) in combination with a fluconazole-impregnated polymethylmethacrylate spacer.
Treatment outcome

The median duration of follow-up of the 4 patients at our institution was 60.4 months, and, for all cases, the median duration of follow-up was 50.7 months after reimplantation.

Eight patients (80%) had no recurrence of candidal PJI after successful delayed reimplantation arthroplasty.

However, 2 patients (20%) developed recurrent candidal infection after delayed reimplantation arthroplasty.
The first relapse occurred in an HIV-positive individual who had developed a TKA PJ I due to *C. parapsilosis* after 2 arthroplasty revisions for a PJ I due to *Staphylococcus hominis* while receiving suppressive therapy with ciprofloxacin and rifampin. The prosthesis was removed and the patient was treated with amphotericin B followed by ketoconazole. Four months later, he underwent reimplantation. One month after undergoing reimplantation arthroplasty, he relapsed while receiving suppressive ketoconazole. In vitro susceptibility to ketoconazole was confirmed. Because of continued joint instability discovered at the time of relapse, he subsequently underwent above-the-knee amputation.
The second patient developed a TKA PJI due to *C. tropicalis* 3 months after undergoing prosthesis implantation.

She relapsed first after a limited excision and debridement. She relapsed again after undergoing resection arthroplasty and reimplantation at 18 days in conjunction with amphotericin B.

This resulted in another resection arthroplasty and arthrodesis, and there was no subsequent evidence of infection. There were no adverse outcomes or subsequent joint revisions documented for the 4 patients treated at our institution.
Discussion

Delayed reimplantation arthroplasty offers the best opportunity for a good functional outcome.
However, only 10 (21.7%) of a total of 46 patients identified in the literature underwent delayed reimplantation arthroplasty for candidal PJI.
Because delayed reimplantation arthroplasty offers the best opportunity for a good functional outcome, we focused on the results of this procedure for treatment of candidal PJI.
Most patients with candidal PJIs underwent permanent prosthesis removal and subsequently had poor functional outcome. This differs from the common practice of administration of 46 weeks of directed antimicrobial therapy followed by delayed reimplantation arthroplasty for total hip and knee PJIs due to other organisms. The overall success rate of delayed reimplantation arthroplasty for total hip and knee arthroplasties varies for all microorganisms (respective ranges, 79%-92% and 63%-89%).
Recurrent infection after delayed reimplantation is a serious complication and often results in permanent removal of the joint prosthesis.

On the basis of the current study, a 20% recurrence rate after 2-stage reimplantation for candidal PJI should be anticipated.

Antifungal therapy appears to be an important component in the successful treatment of candidal PJI.

Recent guidelines recommend antifungal therapy for candidal PJI similar to that recommended in the guidelines for treatment of native joint arthritis and osteomyelitis; the duration of therapy can range from weeks to months, depending on the selected antifungal agent.
Theoretically, early infections treated with thorough irrigation and debridement, with removal of all infected foreign materials, may result in cure for patients who have an intact immune system.
Choice of antifungal agents and duration

The choice of antifungal agents has varied considerably in the cases reported in the literature.
Amphotericin B has been used most commonly and has been the cornerstone of therapy for deep-seated candidal infections.
Guidelines for treatment of candidal native joint arthritis and osteomyelitis suggest use of amphotericin B and/or fluconazole, because treatment with these agents has been shown to be effective in cases reported elsewhere.
Successful treatment of candidal PJI with fluconazole as the sole antifungal agent was reported in 3 cases, and we report an additional case in our series, for a total of 4 cases.

Both clinical and experimental data demonstrate high in vivo activity of fluconazole to most *Candida* species, with good synovial fluid penetration.

Fluconazole has the additional advantage of being less nephrotoxic than amphotericin B.

Although data are limited, therapy with fluconazole appears to be as effective as amphotericin B therapy for susceptible strains when combined with adequate surgical drainage.
The total duration of antifungal therapy necessary for eradication of infection is also unknown.

In the present study, the duration of treatment ranged from 6 weeks to 9 months, with the median being 6 weeks for patients who received amphotericin B and slightly more than 17 weeks for patients who received fluconazole.

Wide variability exists in cases reported elsewhere.
For patients who are infected with susceptible organisms and who have an intact immune system, treatment for a minimum of 6 weeks has been most consistently successful in eradicating infection; eradication should be confirmed by culture prior to reimplantation.
Optimal time to reimplantation

The optimal time to reimplantation for patients with candidal PJI has not been determined, because candidal PJIs are notoriously indolent and there is no consistent test for successful eradication.

Most studies that have looked at the time to reimplantation have indicated that a TKA may be reimplanted sooner than a THA after a bacterial infection.

Although there is considerable variation in the literature regarding the optimal time to reimplantation, successful reimplantation is based on the ability to adequately eradicate the infection.
In the current study, the average time to reimplantation for THA was longer than that for TKA (8.6 versus 2.3 months, respectively) but was consistent with the time to reimplantation for PJIs due to other organisms at our institution during the same time period.

Other investigators have recommended that, for cases of PJI due to unusual or virulent organisms, there should be a longer period of time between resection and reimplantation, because there is no single reliable method to document eradication of infection.
Current guidelines from the Infectious Diseases Society of America for the treatment of candidal PJI suggest that reimplantation may be done after successful eradication of the infection, as defined by the lack of recurrent symptoms while the patient is not receiving therapy. The infection-free interval period suggested in one study, which was determined on the basis of 2 cases of successful hip reimplantation after candidal PJI, was 3 months.
Antibiotic-impregnated cement

Currently, antibiotic-impregnated cement is used in various ways; it is used most commonly in polymethylmethacrylate (PMMA) spacers prior to reimplantation or mixed with cement for fixation during 2-stage reimplantation procedures. The findings of studies regarding its efficacy as primary prophylaxis for bacterial infection have varied and seem to indicate a slight reduction in the overall rate of late infections.
One of the potential drawbacks to the use of antibiotic-impregnated bone cement, however, is the increase risk of development of drug-resistant organisms. However, there is a greater benefit when antibiotic-impregnated bone cement is used in patients undergoing reconstruction after an infection.
In this study, antifungal-impregnated bone cement was used at the time of reimplantation in none of the patients. Although it is not known whether this may be an effective method to reduce the rate of secondary deep fungal infections after reimplantation arthroplasty, fluconazole-impregnated cement possesses anti-	extit{Candida} activity and is an effective adjunctive therapy in a rat model of 	extit{C. albicans} foreign-body osteomyelitis. Further research in this area is necessary.
Lessons learned

On the basis of the lessons learned from treating THA and TKA infections due to bacteria, as well as the information gained from our series, a few points can be made. First, delayed reimplantation arthroplasty can be successfully performed after eradication of candidal PJI. Second, a combined medical and surgical approach that includes antifungal therapy (either fluconazole and/or amphotericin B) and confirmation of an infection-free period of time after the initial surgical approach appears to provide the best chance of a successful reimplantation.
The optimal duration of antifungal therapy and time to reimplantation remain unknown but may be similar to those for PJIs due to other microorganisms. Local antifungal therapy (antifungal-impregnated beads/spacers) may be an effective adjunct to therapy but needs to be studied further.
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