What Is the Success of Treatment of Hip and Knee Candidal Periprosthetic Joint Infection?

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Abstract

Background Fungal infection at an arthroplasty site is rare and poses a therapeutic challenge. To the best of our knowledge, no reports have been published thus far on the success rate of prosthesis reimplantation after fungal prosthetic joint infections.

Questions/purposes We asked: (1) What is the success rate in terms of infection eradication using a two-stage exchange arthroplasty in patients with hip or knee fungal periprosthetic joint infections, particularly focusing on

Candida infections? (2) What patient-, infection-, and treatment-related variables are associated with the success or failure of treatment?

Methods From January 2000 to December 2010, 16 patients with hip or knee candidal periprosthetic joint infections were treated with two-stage exchange arthroplasty at our institute. Treatment success was defined as a well-functioning joint without relapse of candidal infection after prosthesis reimplantation, while treatment failure was defined as uncontrolled or relapse of candidal infection or mortality. Variables, including age, sex, comorbidities, microbiology, antimicrobial agents used, and operative methods, were analyzed. Minimum followup was 28 months (mean, 41 months; range, 28–90 months).

Results At latest followup, the treatment failed to eradicate the infection in eight of the 16 patients, and there were four deaths related to fungemia. Four patients required permanent resection arthroplasty owing to uncontrolled or recurrent candidal infections. All eight patients (50% successful rate) who had their infections eradicated and successful prosthesis reimplantation had prolonged treatment with oral fluconazole before (mean, 8 months) and after (mean, 2.2 months) prosthesis reimplantation. The antifungal therapy correlated with successful treatment. Renal insufficiency, hypoalbuminemia, anemia, and chronic obstructive pulmonary disease were significantly more prevalent in the treatment-failure group than in the treatment-success group.

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Each author certifies that his or her institution approved the human protocol for this investigation, and that all investigations were conducted in conformity with ethical principles of research.

This work was performed at Chang Gung Memorial Hospital, Linkou, Taiwan.

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Conclusions Half of the patients treated with two-stage exchange arthroplasty for fungal periprosthetic joint infections had recurrence or lack of control of the infection. A prolonged antifungal therapy appeared to be essential for successful treatment of candidal periprosthetic joint infections. The presence of renal insufficiency, hypoalbuminemia, anemia, or chronic obstructive pulmonary disease might be associated with a poor outcome.

Level of Evidence Level IV, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

A periprosthetic joint infection is one of the most devastating complications of joint arthroplasty. The most common pathogens involved in periprosthetic joint infections are *Staphylococcus* species, constituting 50% to 60% of all isolates [26, 31]. Fungal infection at the site of joint arthroplasty is rare, and is estimated to occur in approximately 1% of all cases of periprosthetic joint infections. Fungal periprosthetic joint infections are a therapeutic challenge. Several different treatment methods, including antifungal drugs [21], débridement with retained prosthesis [4, 12, 18, 28], resection arthroplasty [35, 39], and two-stage exchange arthroplasty [1, 24, 38], have been reported, with variable outcomes.

Removal of the entire joint prosthesis along with antimicrobial therapy has been recognized as the most reliable method for control of periprosthetic joint infections [1, 17, 22, 36]. Although two-stage exchange arthroplasty has been reported to be successful in the treatment of patients with fungal periprosthetic joint infections [1, 24, 38], some surgeons are reluctant to perform reimplantation owing to the high risk of relapse of infection [35, 39]. However, resection arthroplasty of the hip or knee is known to cause severe Trendelenburg gait as a result of abductor weakness, marked shortening of the limb, joint instability, pain, difficulty in walking, increased energy demand during gait, and abnormal stress on the spine and other joints [8]. Therefore, sequential reimplantation of the prosthesis to restore normal joint function is an attractive therapeutic choice for patients and surgeons.

To the best of our knowledge, no reports have been published thus far on the success rate of prosthesis reimplantation after fungal periprosthetic joint infections. We therefore asked: (1) What is the success rate in terms of infection eradication using a two-stage exchange arthroplasty in patients with hip and knee fungal periprosthetic joint infections, particularly focusing on *Candida* infections? (2) What patient-, infection-, and treatment-related variables are associated with the success or failure of treatment?

Patients and Methods

We retrospectively reviewed our institutional joint arthroplasty database to identify patients who were diagnosed with a hip or knee candidal periprosthetic joint infection at our institution between January 2000 and December 2010. Candidal infection at the site of joint arthroplasty was defined by positive culture tests of two or more samples from joint aspiration or surgical specimens for *Candida* species. The fungi were cultured on Sabouraud dextrose agar and then incubated for up to 4 weeks at 25°C. All periprosthetic joint infections were late chronic infections, judged to be of 3 weeks' duration or longer [31]. Approval for this study was obtained from our institutional review board.

We identified 1120 patients who had hip or knee periprosthetic joint infections at our institute during the study period. Sixteen patients (1.4%) were diagnosed with candidal infections, 12 men and four women, with an average age of 62 years (range, 31–84 years) and an average BMI of 27 kg/m² (range, 20–42 kg/m²) (Table 1). The average time between the date of the index surgery to periprosthetic joint infection diagnosis was 21 months (range, 2–76 months) (Table 1). Minimum followup for patients with a candidal periprosthetic joint infection was 28 months (mean, 41 months; range, 28–90 months).

We reviewed patient characteristics (age, sex, BMI), comorbidities, results of microbiologic studies, antimicrobial agents used, operative methods, and final outcomes in all patients with hip or knee candidal periprosthetic joint infections.

All patients with a hip or knee candidal periprosthetic joint infection were treated initially with resection arthroplasty for infection control. In brief, resection arthroplasty for periprosthetic joint infections included radical débridement, removal of prosthesis, antibiotic-loaded bone cement implantation, and administration of systemic antimicrobial agents for control of joint infection. Articulating and static spacers were used in hip and knee periprosthetic joint infections respectively. Delayed reimplantation of the prosthesis was performed after successful antimicrobial therapy (defined by the absence of signs of infection including no resting pain, no local heat, no local erythema, no discharge sinus, and erythrocyte sedimentation rate and serum C-reactive protein levels resuming normal levels) [34].

All patients were treated with parenteral antifungal drugs selected on the basis of antifungal susceptibility tests conducted after the resection arthroplasty. All *Candida* species were susceptible to fluconazole. Fluconazole (400 mg/day) was administered to every patient with normal renal function. For patients with renal insufficiency, the fluconazole dose was reduced by 50%, by doubling the

Table 1. Summary of patient characteristics

Patient	Age (years)	Sex	Microbe	Comorbidity	Fungemia/bacteremia	Joint	Antibiotic/antifungal impregnated in cement spacer	Time between the date of index surgery until diagnosis (months)	Duration of symptoms (weeks)	Surgeries before reimplantations or permanent resection arthroplasty	Operative procedures	Outcome
1	62	Male	<i>Candida parapsilosis</i> , MSSA	DM	NR	Knee	Vancomycin + piperacillin	6	6	1	Two-stage exchange arthroplasty	Infection cleared
2	77	Male	<i>Candida parapsilosis</i> , MSSA	NR	NR	Knee	Amphotericin B + vancomycin + piperacillin	7	11	1	Two-stage exchange arthroplasty	Infection cleared
3	66	Male	<i>Candida parapsilosis</i>	NR	NR	Hip	Amphotericin B + vancomycin	3	4	2	Two-stage exchange arthroplasty	Infection cleared
4	84	Female	<i>Candida albicans</i>	NR	NR	Knee	Vancomycin + piperacillin	2	3	2	Two-stage exchange arthroplasty	Infection cleared
5	76	Male	<i>Candida parapsilosis</i>	DM, LC	NR	Knee	Vancomycin + piperacillin	35	8	1	Two-stage exchange arthroplasty	Infection cleared
6	35	Female	<i>Candida albicans</i>	SLE	NR	Knee	Amphotericin B + azidothymidine	47	7	1	Two-stage exchange arthroplasty	Infection cleared
7	72	Male	<i>Candida albicans</i>	NR	NR	Knee	Amphotericin B	23	6	1	Two-stage exchange arthroplasty	Infection cleared
8	36	Male	<i>Candida parapsilosis</i> , MSSA	NR	NR	Knee	Amphotericin B + azidothymidine	76	7	1	Two-stage exchange arthroplasty	Infection cleared
9	62	Female	<i>Candida albicans</i> , MSSA	CRI, LC	NR	Hip	Vancomycin + aztreonam	24	11	1	Resection arthroplasty	Resection arthroplasty
10	67	Male	<i>Candida tropicalis</i>	DM, CRI, COPD	NR	Hip	Vancomycin + piperacillin	16	4	1	Resection arthroplasty	Resection arthroplasty
11	66	Male	<i>Candida parapsilosis</i> , MRSA	COPD	NR	Hip	Amphotericin B + vancomycin + amikacin	4	8	2	Resection arthroplasty	Resection arthroplasty
12	67	Female	<i>Candida albicans</i>	DM	<i>Candida fungemia</i>	Knee	Vancomycin + ceftriaxone	17	9	3	Resection arthroplasty	Resection arthroplasty
13	75	Male	<i>Candida albicans</i>	CRI, COPD	<i>Candida fungemia</i>	Hip	Vancomycin + aztreonam	47	4	2	Resection arthroplasty	Dead
14	78	Male	<i>Candida albicans</i> , MSSA	DM, CRI, COPD	NR	Knee	Vancomycin + piperacillin	2	3	1	Resection arthroplasty	Dead

Table 1. continued

Patient	Age (years)	Sex	Microbe	Comorbidity	Fungemia/bacteremia	Joint	Antibiotic/antifungal impregnated in cement spacer	Time between the date of index surgery until diagnosis (months)	Duration of symptoms (weeks)	Surgeries before reimplantations or permanent resection arthroplasty	Operative procedures	Outcome
15	31	Male	<i>Candida albicans</i> , MRSA	DM, RCC, CRI	<i>Candida</i> fungemia, MRSA bacteremia	Hip	Vancomycin + piperacillin	26	4	1	Two-stage exchange arthroplasty	Dead
16	41	Male	<i>Candida albicans</i> , MSSA	DM, COPD, LC	<i>Candida</i> fungemia	Hip	Vancomycin + piperacillin	3	5	1	Resection arthroplasty	Dead

MSSA = methicillin-susceptible *Staphylococcus aureus*; MRSA = methicillin-resistant *Staphylococcus aureus*; DM = diabetes mellitus; NR = not reported; CRI = chronic renal insufficiency; COPD = chronic obstructive pulmonary disease; LC = liver cirrhosis; RCC = renal cell carcinoma, SLE = systemic lupus erythematosus.

dosing interval [7]. In patients with concomitant *Staphylococcus aureus* infections, oxacillin was administered for the methicillin-sensitive *S aureus* (MSSA) strain and vancomycin for the methicillin-resistant *S aureus* (MRSA) strain, along with fluconazole. The antibiotic-loaded bone cement spacer was used in every patient. However, the diagnosis of fungal infection was found in six patients by joint aspirations before the spacer was placed. The amphotericin-impregnated cement spacer was used in only these six patients. The patients had an antibiotic-free period of at least 2 weeks before reimplantation of the prosthesis.

Treatment success was defined as a well-functioning joint without relapse of candidal or any other infection after prosthesis reimplantation during a followup of more than 2 years. Treatment failure was defined as the occurrence of any of the following conditions at any time after the initial surgical procedure: (1) periprosthetic joint infections attributable to the presence of the original microorganism (relapse of infection) or a different strain (reinfection); (2) development of a sinus tract; or (3) death related to the periprosthetic joint infection.

We performed statistical analyses using SPSS® software (Version 10.0; SPSS Inc, Chicago, IL, USA). The Mann-Whitney test was used for analysis with continuous variables and Fisher's exact test was used for dichotomous variables. Statistical significance was set at a probability less than 0.05.

Results

At latest followup, infection recurred or was not controlled in eight of the 16 patients in this series, and there were four deaths related to fungemia (Table 1). Among these 16 patients, seven had uncontrolled or recurrent infections after the first-stage operations and were unable to have prosthesis reimplantation. The other nine patients underwent delayed prosthesis reimplantation. Among them, eight had a well-functioning revision total joint arthroplasty without any sign of infection relapse at a minimum followup of 2 years. One patient had recurrent candidal infection 18 months after prosthesis reimplantation and eventually died of uncontrolled candidemia and MRSA bacteremia. Among the patients who did not undergo prosthesis reimplantation, four had repeat débridement owing to recurrent candidal infection. Among these four patients, poor medical condition (two with severe chronic obstructive pulmonary disease, one with Child's Class C liver cirrhosis, and one with poor control of diabetes mellitus) made them unable to tolerate further major reconstruction surgery and they required permanent resection arthroplasty. In addition, three patients died owing to uncontrolled candidal infection and deteriorating candidemia

Table 2. Summary of therapeutic approaches

Variable	Treatment success group (n = 8)	Treatment failure group (n = 8)	p value
Cement spacer (number of patients)			
Amphotericin-loaded cement spacer	5	1	0.119
Nonamphotericin-loaded cement spacer	3	7	
Duration of parenteral antifungal drug after first-stage operation (days)*	22 (13–40)	16 (12–30)	0.167
Duration of parenteral antifungal drug (fluconazole) after second-stage operation (days)*	9 (7–19)	NA	
Duration of oral antifungal drug (fluconazole) after first-stage operation (months)*	8 (3–18)	0.5 (0–2.5)	0.001
Duration of oral antifungal drug (fluconazole) after second-stage operation (months)*	2.2 (1.5–3)	NA	

* Values are expressed as mean, with range in parentheses; NA = not applicable.

Table 3. Summary of comorbidities

Comorbidities	Treatment success (n = 8)	Treatment failure (n = 8)	p
Number of comorbidities			
Liver cirrhosis	1	2	0.569
Chronic renal insufficiency (serum creatinine > 1.6 mg/dL)	0	5	0.026 [†]
Diabetes mellitus	2	5	0.315
Chronic obstructive lung disease	0	5	0.026 [†]
Systemic lupus erythematosus	1	0	1
Malignancy	0	1	1
Hemoglobin (g/dL)	13 (10–15)*	9 (7–13)*	0.046 [†]
Hypoalbuminemia (serum albumin < 3 g/dL)	1	6	0.041 [†]

* Values shown are means, with ranges in parentheses. [†]p < 0.05.

sepsis. The outcome in all patients with fungemia or bacteremia was treatment failure, with resection arthroplasty in one and death in three.

All patients who underwent successful prosthesis reimplantation after candidal periprosthetic joint infections had received prolonged oral fluconazole therapy (400 mg/day; mean, 8 months; range, 3–18 months) before reimplantation of the prosthesis, compared with patients with treatment failure (mean, 0.5 months; range, 0–2.5 months) (p = 0.001) (Table 2). In addition, after prosthesis reimplantation, all patients with successful treatment received parenteral antifungal therapy for 9 days (range, 7–19 days), and subsequently oral antifungal drugs for 2.2 months (range, 1.5–3 months). No significant differences were observed in terms of infection eradication

Table 4. Summary of microbiologic evaluation

Variable	Treatment success group (n = 8)	Treatment failure group (n = 8)	p value
Pathogens (number of patients)			
<i>Candida albicans</i>	3	6	0.315
<i>Candida parapsilosis</i>	5	1	0.119
<i>Candida tropicalis</i>	0	1	1
Candidemia/bacteremia (number of patients)	0	4	0.077
Concomitant bacterial infections (number of patients)	3	5	0.619

related to differences in the parenteral antibiotic regimen. The duration of parenteral antifungal therapy was 22 days (range, 13–40 days) for patients with treatment success and 16 days (range, 12–30 days) for patients with treatment failure (p = 0.167) (Table 2). Factors related to success or failure of treatment were analyzed. Regarding comorbidities, patients with chronic renal insufficiency (creatinine level > 1.6 mg/dL) [19], chronic obstructive pulmonary disease, anemia, or hypoalbuminemia had a significantly higher rate of unsuccessful outcomes than those without these comorbidities (Table 3). On microbial analysis, no significant differences were noted in the prevalence of the *Candida* species between the treatment-success and treatment-failure groups (Table 4). However, the incidence of fungemia or bacteremia was higher in the treatment-failure group (four of eight) than in the treatment-success group (zero of eight), although this difference was not significant (Table 4).

Discussion

A periprosthetic joint infection is one of the most devastating complications of joint arthroplasty. A fungal infection at the site of a joint arthroplasty is rare and estimated to occur in approximately 1% of all cases of periprosthetic joint infections. Fungal periprosthetic joint infections are a therapeutic challenge. To the best of our knowledge, no reports have been published thus far on the success rate of prosthesis reimplantation after fungal periprosthetic joint infections. We therefore asked the following questions: (1) What is the success rate in terms of infection eradication using a two-stage exchange arthroplasty in patients with hip and knee fungal periprosthetic joint infections, particularly focusing on *Candida* infections? (2) What patient-, infection-, and treatment-related variables are associated with the success or failure of treatment? Delayed reimplantation and a long course of oral antifungal therapy were associated with the patients whose treatment was successful in this small series. Meanwhile, chronic renal insufficiency, hypoalbuminemia, anemia, and chronic obstructive pulmonary disease were found to be predictors of poor outcomes in patients with candidal periprosthetic joint infections.

The major limitation of our study was the small sample size. It was a retrospective study and was performed during an extended period which resulted in variability in several factors, including operating surgeons, antibiotic regimens, duration of antibiotic therapy, and time between resection arthroplasty and reimplantation. The rarity of cases associated with candidal periprosthetic joint infections made it impossible to perform a clinically randomized trial. The lack of reliable antifungal medications for systemic and local therapy for candidal periprosthetic joint infections poses a therapeutic challenge for every orthopaedic surgeon. There was potential bias in our study regarding the duration of antifungal treatment. The shorter duration of treatment in the group with failed treatment could be attributable to the mortalities which made the patients unable to have long-term antifungal treatment. However, despite these limitations, we believe our findings are of value as the study provides rare outcome data regarding resection arthroplasty for the treatment of candidal periprosthetic joint infections.

Most of the published articles on fungal periprosthetic joint infections have been case reports [4, 6, 9, 12, 13, 16, 18, 19, 21, 28, 35, 37, 39]. Owing to the rarity of fungal periprosthetic joint infections, the outcome of this serious complication has not been widely reported in the literature. Two-stage exchange arthroplasty provides an 80% to 100% success rate for bacterial periprosthetic joint infections [5, 10, 15, 17, 29, 36]. However, using this therapeutic strategy, only eight of the 16 patients with candidal

periprosthetic joint infections in our study had successful outcomes. Four of the 16 patients had a final outcome of permanent resection arthroplasty owing to recurrent candidal infection, and four of the 16 patients died as a consequence of the periprosthetic joint infection. This study is a retrospective review of fungal periprosthetic joint infections treated with a similar protocol, ie, resection arthroplasty combined with or without delayed prosthesis reimplantation. Using a similar therapeutic protocol, Anagnostakos et al. [1] reported seven cases of fungal hip and knee periprosthetic joint infections. Only two of the seven (28%) had successful prosthesis reimplantation without relapse of fungal infection.

Based on our results and those reported in the literature [1, 4, 12, 18, 19, 21, 24, 28, 35, 38, 39], candidal periprosthetic joint infections are associated with variable outcomes. All of our patients who had successful outcomes were treated with oral antifungal drugs (fluconazole) for a prolonged time, before (mean, 8 months) and after (mean, 2.2 months) prosthesis reimplantation. A long period of oral antifungal treatment has been recognized as being an essential factor for the success of staged reimplantation after a fungal periprosthetic joint infection [24]. In our study, patients with successful prosthesis reimplantation received at least 1.5 months of oral fluconazole therapy. Phelan et al. [24] administered antifungal therapy after resection arthroplasty for 6 weeks to 9 months in four patients who underwent two-stage reimplantations. Fluconazole has a high oral bioavailability and superior bone and synovial penetration capacity [2, 6]. Infectious Diseases Society of America guidelines suggest prolonged therapy with antifungal agents for the treatment of candidal osteomyelitis should be 6 to 12 months and for treatment of candidal septic arthritis at least 6 weeks [23], suggesting eradication of a candidal infection after resection arthroplasty by prolonged oral antifungal therapy can help to achieve a high success rate of reimplantation and is essential to achieve a successful outcome of fungal periprosthetic joint infections. Resection arthroplasty in conjunction with systemic antifungal agents and followup oral fluconazole therapy appears to be the best approach for successful reimplantation and a satisfactory functional outcome. Antibiotic-loaded bone cement now is considered the gold standard for the treatment of bacterial periprosthetic joint infections [5]. However, the efficacy of antifungal-loaded cement spacers in the treatment of fungal periprosthetic joint infections is controversial. The placement of amphotericin B-loaded cement spacers has been reported to successfully eradicate fungal periprosthetic joint infections [37]. However, amphotericin B has been found to form covalent crosslinks in the polymethylmethacrylate matrix and does not elute from the polymethylmethacrylate bone cement [14]. This poor elution from the bone cement

may explain why, in the current study, patients with amphotericin B-impregnated cement spacers did not have a better outcome than those without such spacers.

Immunocompromise is recognized as a major cause of fungal infection. Diabetes mellitus [20], liver cirrhosis [25, 27], malignancy [32], and hypoalbuminemia (albumin < 3.0 g/dL) [33] have been shown to lead to higher infection rates in joint arthroplasty. Meanwhile, renal function, nutritional status, and pulmonary function are known to be important in the host's ability to respond to the treatment of musculoskeletal infection [22, 26]. Host factors, such as immune and nutritional status, not only predispose patients to fungal infection but also can determine the final outcome [3, 11, 30]. Eleven of the 16 patients in our study (69%) had at least one systemic disease associated with compromised immune function. Chronic renal insufficiency, hypoalbuminemia, anemia, and chronic obstructive pulmonary disease were significantly more prevalent in the treatment-failure group than in the treatment-success group. The compromised immunity may predispose the host to fungal infection. The high prevalence of compromised immunity may have contributed to the high failure rate of candidal periprosthetic joint infections treatment in our patients.

The overall rate of mortality attributable to candidal periprosthetic joint infections was 25%. Radical débridement combined with first-stage resection arthroplasty and prolonged antifungal therapy enabled successful delayed prosthesis reimplantations in 50% of our patients. The presence of renal insufficiency, hypoalbuminemia, anemia, or chronic obstructive pulmonary disease was associated with a poor outcome. Prolonged fluconazole therapy was found to be an essential factor for eradication of candidal periprosthetic joint infections. In the consideration of candidal periprosthetic joint infections treatment, two-stage exchange arthroplasty combined with prolonged oral fluconazole therapy (at least 12 weeks after the first-stage resection arthroplasty and at least 6 weeks after prosthesis reimplantation) is highly recommended.

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