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Success Rate of Fungal Peri-Prosthetic Joint Infection Treated by 2-Stage Revision and Potential Risk Factors of Treatment Failure: A Retrospective Study

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Background: The aim of this study was to investigate the success rate of fungal peri-prosthetic joint infection treated by 2-stage revision and related factors of treatment failure to offer a better treatment protocol.





Material/Methods: We reviewed 18 joints (13 knees and 5 hips) of 17 patients (10 women and 7 men) diagnosed with fungal peri-prosthetic joint infection from January 2000 to June 2015 at our institute. The mean follow-up was 65.1 months (range, 25–129 months). All joints were treated with complete debridement, implantation of antifungal-loaded cement spacers, at least 6 weeks of parenteral antifungal agents, and delayed reimplantation.

Results: Notably, 15 joints were infected with *Candida*, and molds were isolated in 3 joints. The median duration of resection arthroplasty and reimplantation was 33.9 weeks (range, 12–132 weeks). Thirteen (10 knees and 3 hips, 72.2%) of the 18 joints (13 knees and 5 hips) had no recurrent or persistent infection, while the remaining 5 joints (3 knees and 2 hips, 27.8%) failed to control infection after reimplantation of prosthesis or spacer. The long interval between prosthesis resection and reimplantation (69 weeks vs. 23.1 weeks, $p=0.240$) and mixed bacterial infection (80% vs. 46.2%, $p=0.314$) were associated with higher failure rate.

Conclusions: Debridement with the retention of the prosthesis is not an ideal treatment protocol for fungal peri-prosthetic joint infection; thus, a two-stage revision could be valid. We suggest that 6 weeks of parenteral antifungal agents are necessary, and 6 subsequent weeks of oral antifungal treatment is also important. We do not recommend that the two-stage revision be performed on patients who have more than 2 host risk factors.

MeSH Keywords: **Arthroplasty • Candida • Joints • Risk Factors**

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Background

Peri-prosthetic joint infection (PJI) is one of the most complex and debilitating complications of total joint replacement, which is the first and third major cause of revision following total knee arthroplasty and total hip arthroplasty, respectively [1–4]. *Staphylococcus* species are major pathogens, accounting for 50%–60% of all isolates [5,6].

Fungal PJI is rare and occurs in approximately 1% of all PJI [7,8], representing a diagnostic and therapeutic challenge because of a lack of established guidelines [7]. Chronic infections are typically treated in North America with a two-stage exchange protocol. Numerous studies have reported that two-stage revision surgery and articulating spacers can result in a rate of infection control as high as 95% in patients with PJI [9–12], but whether this protocol is efficacious for fungal PJI remains controversial. Hwang et al. reported on 30 two-stage revision procedures for fungal PJI, and only 2 knees became reinfected at the last follow-up date [13]. Garcia-Oltra et al. concluded that treatment with fluconazole and debridement or two-stage replacement with a spacer was associated with a high failure rate [14].

In 2002, McPherson et al. reported the first clinical staging system for PJI, which can divide patients into different gradations according to infection type, host status, and extremity status [15]. This staging system is helpful in evaluating fungal PJI and treatment algorithms.

The purpose of the present retrospective study was: (1) to determine the success rate of 2-stage exchange arthroplasty based on the patients' grades according to McPherson's staging system and (2) to assess which factors are associated with failure of treatment.

Material and Methods

Following Institutional Review Board approval, from January 2000 to June 2015, we retrospectively reviewed 18 joints (13 knees and 5 hips) of 17 patients (10 women and 7 men) who were identified infection by fungal at our institute. One of the female patients had infected bilateral knees. The average age of diagnosis was 61.2 (range, 42–78) years, and the mean follow-up was 65.1 months (range, 25–129 months). We defined fungal PJI as positive culture tests of 2 or more samples from joint aspiration or intraoperative specimens. The fungi were incubated on TTC-Sabourand's medium.

The following information was collected through medical records and telephone follow-up: age, sex, body mass index (BMI), site of infection, pathogenic fungi, other microorganisms

cultured, laboratory values (CRP and ESR), operative method, local and system antifungal agents, interval between prosthesis resection and reimplantation, prior operation times, time from primary total joint arthroplasty to the diagnosis of fungal PJI, comorbidity and grade of each patient according to McPherson's staging system, final outcomes and patients' satisfaction, and duration of follow-up (Table 1).

We treated all the patients with the two-stage protocol. After removal of all components of the infected joint, a thorough debridement was performed. Subsequently, we implanted antibiotic-loaded bone cement spacers and systemically administered antifungal agents. An articulating spacer was applied for 12 knees and 4 hips, and only 2 irrigated static spacers were used. The antibiotic type and doses added in bone cement were used at the discretion of the operating surgeon. Only 8 spacers contained antifungal agents and Vancomycin because of specific species isolated through preoperative aspiration, and 2 of these spacers were irrigated static spacers. A total of 9 patients had negative culture results at preoperative aspiration and used Vancomycin-loaded bone cement spacer. One of the patients had resected components and implanted spacer performed at an outside institute; thus, whether antibiotic-loaded or not in the spacer was unknown (Table 2). Intraoperative synovial fluid and suspicious tissue specimens were collected for microbiological culture (aerobic, anaerobic, *Mycobacterium*, and fungal) and pathological examination. Subsequently, patients received parenteral antifungal agents according to sensitivity test of the culture for at least 6 weeks, and most of them were followed by oral fluconazole or rifampicin. Reimplantation was controlled until antifungal agents were paused for at least 2 weeks and inflammatory markers, such as ESR and CRP, declined to normal.

We defined treatment success as successful reimplantation without "persistent infection" or "reinfection" during the follow-up. Treatment failure was defined as the occurrence of any of the following conditions at any time after the initial surgical procedure: (1) peri-prosthetic joint infections attributed 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 peri-prosthetic joint infection [16]. According to McPherson's staging system, we grouped type A, based on host risk factors, into a low-risk group, and types B and C into a high-risk group.

The descriptive statistics are reported as the number (percentage) or mean (range), as appropriate. We compared binary variables by chi-square and Fisher exact tests. A paired *t* test was used to compare the differences between preoperative and postoperative HSS/Harris scores, as well as range of motion (ROM). Analyses were performed using SPSS software (Version 19.0; SPSS Inc., Chicago, IL, USA).

Table 1. Summary of 17 patients (18 joints) demographic data.

Patient	Age/ Sex	BMI (kg/m ²)	Joint	Pathogen Organism	A1	Comorbidity	Mcperson classification	A2	CRP at presentation (mg/l)	ESR at presentation (mm/h)	IL-6	HSS/ Harris	ROM (°)
1	63/F	28.9	Knee	<i>Aspergillus</i> spp.	26	None	A3	3	4.99	25	3.87	40	45
2	78/F	18.6	Knee	<i>Candida tropicalis</i> , <i>Candida parapsilosis</i>	12	None	A2	3	0.317	29	<2.0	48	60
3	63/F	23.8	Knee	<i>Candida albicans</i>	10	Hypertension, diabetes, Rheumatoid	C2	1	0.317	54	6.84	61	70
4	58/F	31.3	Knee	<i>Candida freyschussii</i>	12	None	A2	2	0.95	75	–	35	50
5	63/M	34.2	Knee	Gram- positivebacteria, Rapid mycobacterium, <i>Aspergillus</i>	1.5	Hypertension, diabetes, Respiratory sleep pause syndrome	C3	2	10	92	–	58	85
6	52/F	24.8	Knee	<i>Acremonium strictum</i>	42	None	A2	1	0.348	17	8.46	68	80
7	64/M	22.5	Knee	<i>Candida glabrata</i>	14	Coronary heart disease	A2	2	–	–	–	42	45
8	63/F	24	Knee	<i>Candida parapsilosis</i>	29	Coronary heart disease	A1	1	0.699	90	10.81	53	135
9	63/F	24	Knee	<i>Candida parapsilosis</i>	29	Coronary heart disease	A1	1	0.699	90	10.81	52	125
10	54/M	28.7	Knee	<i>Candida parapsilosis</i> , Human <i>Staphylococcus</i>	5	None	A2	2	7.49	25	41.63	48	130
11	67/M	24	Knee	<i>Candida parapsilosis</i>	5	Hypertension	A2	2	0.48	20	–	55	100
12	69/F	22.6	Knee	<i>Candida albicans</i> , <i>Staphylococcus cohnii</i>	3	Hypertension, diabetes	B1	2	–	–	–	–	–
13	66/M	29.41	Knee	<i>Candida parapsilosis</i> , <i>Staphylococcus epidermidis</i> , <i>Pseudomonas aeruginosa</i>	46	None	A1	2	1.65	21	–	49	60
14	62/F	22.31	Hip	<i>Candida tropicalis</i> , <i>Staphylococcus epidermidis</i> , <i>Escherichia coli</i>	36	None	A2	3	9.11	38	–	62	–
15	42/M	24.7	Hip	<i>Candida albicans</i> , <i>Acinetobacter lwoffii</i>	10	None	A2	2	11.9	130	–	48	–
16	53/F	16.6	Hip	<i>Candida albicans</i> , <i>Staphylococcus aureus</i>	8	Diabetes	B2	6	6.23	61	–	45	–
17	43/F	18.3	Hip	<i>Candida albicans</i> , <i>Enterococcus faecalis</i>	84	Gallbladder excision	A2	4	6.3	86	–	43	–
18	78/M	25.6	Hip	<i>Candida glabrata</i> , Gram negative bacilli	1	None	A2	4	6.02	67	–	37	–

The value of ESR, CRP, HSS, ROM was measured before arthroplasty resection. “–” – unknown. Number of prior operation before resection arthroplasty include the first total joint arthroplasty and irrigation and debridement times before resection arthroplasty. A1 – Symptom duration, time from symptom appearance to prosthesis resection (months). A2 – No. of prior operation before resection arthroplasty

Table 2. Treatment and outcome of 17 patients (18 joints) with fungal PJI.

Patient	Operative procedures	Time between stage (w)	Systemic antimicrobial therapy (w, before reimplantation)	Systemic antimicrobial therapy (w, after reimplantation)	Impregnation of bone cement	Complication	Follow-up (months)	HSS/Harris	ROM (°)	Satisfaction	Outcome
1	Two-stage	28	I.V. F 24w	I.V. F 4w + Oral R 6w	V1 6 g + M 2g +BC 80 g	None	62+18	91	90	Very satisfied	success
2	Two-stage	12	I.V. F 6w + V1 6w +Oral R 12w	I.V. F 6w + V1 6w +Oral R 8w	V1 4 g + M 2 g + V2 0.8 g + BC 80 g	Leukopenia	28	87	120	Very satisfied	success
3	Two-stage exchange spacer	64 (#1) 68 (#2)	#1: I.V. V2 6w + Oral F 12w #2: I.V. V2 4w + Oral F 8w		#1: V1 2 g + A1 1g + BC 120 g #2: V1 4 g + V2 3 g + BC 120 g	None	26	60	0	satisfied	failure
4	Two-stage	12	I.V. F 6w+ Oral F 6w	I.V. C1 4w+ Oral F 8w	V1 12 g + BC 120 g	1*	56+18	91	30	satisfied	success
5	Debridement and Four-stage exchange arthroplasty	12 (#1) 28 (#2) 16 (#3)	#1: I.V. V1 2w #2: I.V. A2 8w+ Oral C2 4w + A3 4w #3: I.V. F 8 weeks	I.V. F 4w	#1: V1 15 g + BC 80 g #2: M8 g + A3 8g + A2 1 g + BC 80 g #3: M 4 g + BC 80 g	None	51	91	120	Very satisfied	failure
6	Debridement and Two-stage	36	I.V. V2 6w +Oral F 12w	I.V. V2 2w + Oral F 6w	V1 4 g + M 3 g + V2 0.4 g + BC 120 g	None	30	60	90	Not satisfied	success
7	Debridement and Two-stage	40	I.V. F 6w + V1 6w + Oral I 12w	I.V. F 1w	F 4 weeks + V1 4w (Irrigation)	None	129	91	90	Very satisfied	success
8	Two-stage	12	I.V. F 6w +Oral F 6w	I.V.F 2w +Oral F 8w	V1 12 g + BC 80 g	None	44	87	120	satisfied	success
9	Two-stage	24	I.V. F 8w +Oral F 14w		V1 12 g + BC 80 g	None	44	84	110	satisfied	success
10	Debridement and Two-stage	16	I.V. F 6w +Oral F 6w	I.V. V2 6w + Oral F 6w (After irrigation and debridement)	V1 6 g + V2 0.8 g + BC 80 g	Abnormal sound	32	86	120	satisfied	failure
11	Two-stage	16	I.V. F 6w	I.V. F 4w	V1 6 g + A1 0.6 g + BC 120 g	None	48+18	90	90	satisfied	success
12	Two-stage	24	I.V. F 6w (Other institute treatment)	I.V. F 6w + Oral F 6w	–	None	25	51	90	Not satisfied	success
13	Debridement and Two-stage	52	I.V. F 6w + V1 6w + Oral F 6w	I.V. F 4w + Oral F 8w + R 12w	V1 10 g + A1 2.5 g+ BC 80 g	None	64	85	90	satisfied	success
14	Two-stage	–	I.V. F 4w + V1 4w + Oral I 8w	I.V. F 4w + Oral I 8w (No reimplantation)	F 4 weeks + V1 4w (Irrigation)	None	118	82	–	Not satisfied	failure
15	Two-stage	12	I.V. F 6w + Oral F 6w	I.V. F 4w	V1 8 g + BC 80 g	None	75	92	–	satisfied	success
16	Double Two-stage First revision at outside institution	14	I.V. F 6w + Oral F 6w	I.V. F 4w	V1 12 g + BC 120 g	None	118	87	–	satisfied	success
17	Two-stage	18	I.V. F 4w + Oral F 12w	I.V. F 4w	V1 8 g + M 4 g +BC 80 g	Nerve injury	97	86	–	satisfied	success
18	Two-stage exchange spacer and prosthesis resection	72	#1: I.V. F 12w + A1 8w #2: I.V. V2 4w + L2 4w +Oral F 8w	C1 6 weeks (Irrigation after spacer resection)	#1: V1 12 g + BC 100 g #2: V1 12 g + BC 100 g	None	71	62	–	Not satisfied	failure

#1 – first spacer to second spacer; #2 – second spacer to third spacer or reimplantation; #3 – third spacer to reimplantation.
A₁ – Amphotericin B; A₂ – Amikacin; A₃ – Azithromycin; BC – bone cement: (1 g gentamicin/40 g bone cement); C₁ – Caspofungin; C₂ – Ciprofloxacin; F – fluconazole; I – Itraconazole; L₁ – Levofloxacin; L₂ – Linezolid; M – Meropenem; R – rifampicin; V₁ – Vancomycin; V₂ – Voriconazole; 1* – Peri-prosthetic fracture + Renal insufficiency + Leukopenia; “–” – unknown.

Results

Clinical features

A total of 10 patients (11 knees) had the symptom of pain and swelling: some patients felt warmth and redness locally, 5 patients (2 knees and 3 hips) had sinus tract, and 1 patient knee had internal instability. The range of motion (ROM) of the 12 knees (1 patient resected arthroplasty at another hospital), prior to the resection of arthroplasty, was 82 degrees. According to McPherson's classification, 2 patients (3 knees) belonged to IIIA1, 10 patients were categorized as IIIA2, IIIA3, IIIB1, IIIB2, or IIIC2, and 1 patient was categorized as IIIC3. The mean symptom duration was 20.7 months (range, 1–84 months).

Microbiology and laboratory findings

In total, 15 patients (1 patient had a bilateral knee infection) were infected with *Candida*, and 6 (6 knees) patients showed *Candida parapsilosis*, which contained 3 mixed infections: *Candida tropicalis*, human *Staphylococcus* and *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa*. In 5 patients, the causative organism identified was *Candida albicans*; however, 4 patients showed a mixture of other episodes, including *Staphylococcus cohnii*, *Acinetobacter lwoffii*, *Staphylococcus aureus*, and *Enterococcus faecalis*. Two patients had *Candida glabrata* infections, and one of these patients was simultaneously infected with Gram-negative bacilli. Another 2 patients had *Candida freyschussii* and *Candida tropicalis* infections, and one of these patients showed a mixed infection with *Staphylococcus epidermidis* and *Escherichia coli*. Molds were isolated in 3 patients, including *Aspergillus* in 2 patients, and one of these patients was coinfecting with Gram-positive bacteria and rapid *Mycobacterium*, while the other patient was infected *Acremonium striatum*. Prior to resection of the prosthesis, ESR and CRP was detected in 16 patients (11 knees and 5 hips), and the average value of CRP and ESR was 4.4 mg/dL (range, 0.3–11.9 mg/dL) and 57.5 mm/h (range, 17–130 mm/h), respectively. IL-6 was detected in 7 patients (7 knees and 1 hip), and the mean level at presentation was 12.77 pg/ml (range, 2–41.63 pg/ml).

Surgical treatment

Five patients underwent irrigation and debridement (ID) with prosthesis reservation; however, because of uncontrolled infection, all of these patients had components removed subsequently. The other 13 patients (8 knees and 5 hips) had resected prosthesis at the initial surgery. Thus, 18 spacers were inserted in total. According to preoperative aspiration, 8 patients received antifungal-loaded spacers because of positive fungal cultures, whereas another 9 patients (4 knees and 5 hips) received Vancomycin-loaded or other antibacterial-loaded

spacers. Additionally, 2 irrigated static spacers were implanted, and we irrigated with fluconazole and Vancomycin for 4 weeks. One patient underwent index surgery at another institution, and whether antibacterial agents were added in bone cement is unknown.

Antifungal therapy

Most of the patients were subjected to 6 weeks systemic antimicrobial therapy after the spacer implantation. Except for 1 patient, who was administered Vancomycin for 2 weeks after resection arthroplasty, and whose preoperative samples cultured Gram-positive bacteria, the remaining patients were administered antifungal agents. Fluconazole was intravenously injected into 15 patients (10 knees and 5 hips) for a minimum of 2–24 weeks, 12 patients (8 knees and 4 hips) subsequently received oral fluconazole or Itraconazole for 6–14 weeks, and 4 patients received combined Vancomycin and/or Rifampicin for 6 weeks for the coexist bacteria. Voriconazole was parenterally administered to 2 patients for 6 weeks, followed by oral fluconazole treatment for 12 weeks.

After the systemic administration of antifungal agents, ESR and CRP values were measured until they declined to normal prior to reimplantation; otherwise, the procedure was not conducted. The median duration of resection arthroplasty and reimplantation was 33.9 weeks (range, 12–132 weeks). A total of 14 patients (11 knees and 3 hips) underwent prosthesis reimplantation, and 13 patients (10 knees and 3 hips) ultimately showed success, while 1 patient experienced recurrent infection after successful reimplantation. The patients were subjected to further debridement and exchanged tibial-bearing inserts. One patient had spacer resection and no reimplantation at last follow-up. However, 3 patients (2 knees and 1 hip) underwent irrigation and debridement, and the spacer was exchanged again due to recurrent or persistent infection (Figure 1). Delayed reimplantation was performed in one of the 3 patients, while another patient did not have the prosthesis changed because of the financial burden, and the other patient had the spacer changed a third time due to recurrent infection.

Risk factors

According to the univariate analysis, patients who have more than 1 risk factor of host and extremity are more likely to fail (15.4% vs. 40%, $P=0.53$, 69.2% vs. 100%, $P=0.278$) (Table 3) but the difference was not significant. In the treatment failure group, patients had a longer interval between prosthesis resection and reimplantation (mean, 69 weeks; range, 16–132 weeks) than in the success group (mean, 23.1 weeks; range, 12–40 weeks) ($P=0.240$). The mixed infection rate was 80% in the treatment failure group and 46.2% in the success group

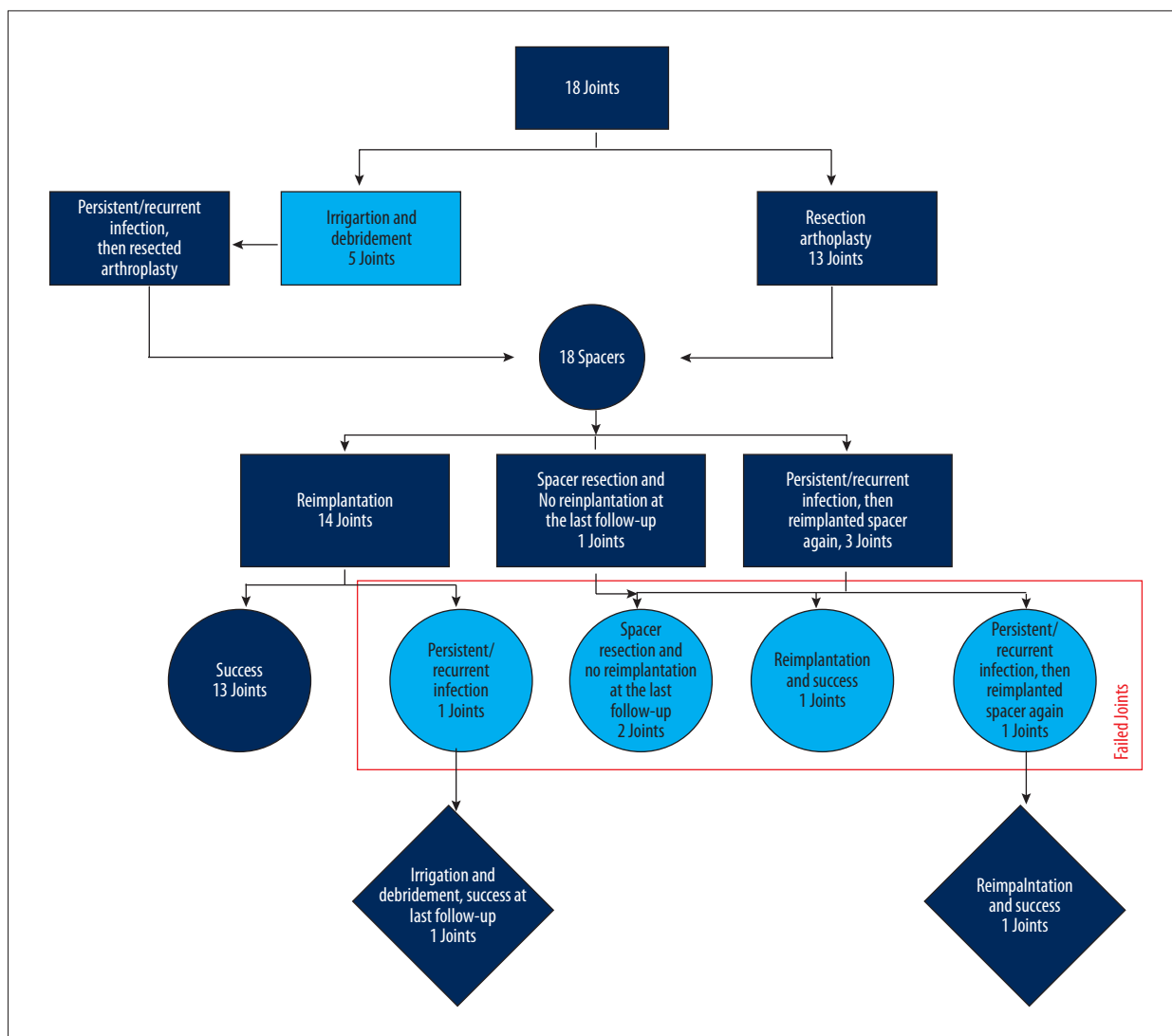


Figure 1. A flowchart of 18 joint outcomes at our institute from January 2000 to June 2015.

($P=0.314$). However, we did not find any significant difference between individuals with diabetes mellitus and hypertension and heart disease comorbidities and individuals who did not have these diseases. Thus, debridement history, infection site, and presence of sinus tract may not be treatment failure risk factors.

Outcome

At the time of follow-up at a mean of 65.1 months (range, 25–129 months) after 2-stage reimplantation, 13 (10 knees and 3 hips, 72.2%) of the 18 joints (13 knees and 5 hips) did not experience recurrent or persistent infection, 5 (3 knees and 2 hips, 27.8%) of the 18 joints (13 knees and 5 hips) failed to control infection after reimplantation prosthesis or spacer, and all patients underwent further surgical intervention. No patients had signs of infection at the latest follow-up, and no

above-the-knee amputation, arthrodesis, or resection of arthroplasty occurred. The failure rate was 21.4% in the low-risk group and 50% in the high-risk group. The HSS/Harris score increased from 50.8/47 (range, 35–68) to 81.1/81.8 (range, 51–92), and the range of motion (ROM) improved from 82.1° (range, 45°–135°) to 89.2° (range, 0°–120°). A total of 14 patients (11 knees and 3 hips, 77.8%) were satisfied with the revision outcome.

Complications

There was no dislocation or fracture of the bone cement spacer. Two patients had leukopenia after using antifungal agents, and 1 of these patients also had renal insufficiency and peri-prosthetic fracture. At the latest follow-up, 1 patient had an unexplained abnormal sound.

Table 3. The impact of debridement and irrigation history, McPherson classification, and infection type on the outcome.

Variable	Success (n=13)		Failure (n=5)		Univariate analysis P
Demographic data					
Age (range)	60.1	(42–78)	64	(54–78)	0.462
Sex (Male, %)	4	(30.8%)	3	(60.0%)	0.326
BMI (kg/m ²)	23.8	(16.6–31.3)	26.9	(22.3–34.2)	0.204
Prosthesis age (month)	25	(1–84)	10.7	(1–36)	0.223
Interval between prosthesis resection and reimplantation(weeks)	23.1	(12–40)	69	(16–132)	0.240
Antifungal agents in spacer*	5	(41.6%)*	3	(60.0%)	0.620
Debridement history	3	(23.1%)	2	(40%)	0.583
Mixed infection	6	(46.2%)	4	(80.0%)	0.314
Infection site (Hip)	3	(23.1%)	2	(40%)	0.583
Sinus tract	3	(23.1%)	2	(40%)	0.583
Diabetes mellitus	2	(15.4%)	2	(40%)	0.533
Hypertension/heart disease	5	(38.4%)	2	(40%)	1.00
Mcperson grade					
Host B+C	2	(15.4%)	2	(40%)	0.533
Extremity 2	9	(69.2%)	5	(100%)	0.278

* One patient had the first operation in other institute, whether the spacer contained antifungal agents or not is unknown. Therefore, in the success group, there were 5 joints that were mixed with antifungal agents in the spacer (41.6%, 5/12).

Discussion

Fungal PJI is a rare entity that occurs in approximately 1% of all PJI. With increasing numbers of total knee arthroplasties (TKA) and total hip arthroplasties (THA) being performed, the incidence of fungal PJI may be increasing [7,8,13,17,18]. Additionally, the therapeutic and diagnostic guidelines for fungal PJI have not been established, posing a challenge to the orthopedic surgeon. McPherson et al. constructed a classification system based on infection type, host status, and extremity risk factors [15], and to the best of our knowledge, there are no published reports concerning the fungal PJI success rate on the basis of this classification system. We defined the results of 2-stage revision for fungal PJI according to McPherson's staging system.

Most fungal PJIs are chronic infections, rarely accompanied by acute symptoms due to the indolent character of fungi. All patients in our hospital were classified as late chronic infection (type III), and most had pain and swelling, with or without warmth and redness. These common infection symptoms were found to be statistically insignificant in previous reports [19,20].

In the present study, the median duration of symptoms was 20.8 months (range, 1–84 months), consistent with results reported by Brooks (median, 14 months) [18] and Hwang (median, 19.6 months) [13], but shorter than the findings reported by Azzam (median, 29 months) [7] and Cobo et al. (median, 33 months) [17]. This finding may be related to their intrinsic aggressiveness, as fungal infections are indolent and do not likely account for the observed symptoms.

In contrast to most of the fungal infection caused by *Candida albicans* [17], *Candida parapsilosis* was the major pathogen in the present study, consistent with Hwang and Wang [13,21]. However, 10 patients (5 knees and 5 hips) also had other fungal or bacterial infections, which may be incubated from preoperative joint aspiration or intraoperative samples. There is no standard definition of PJI, and the Infectious Disease Society of America (IDSA) and the Musculoskeletal Infection Society (MSIS) [22,23] use 2 different definitions. Therefore, considering the complexity of fungi, extending the incubation time is necessary for suspicious infections. Furthermore, more than 4 samples were recommended for seeding onto 3 different culture media [24].

Debridement with the retention of the prosthesis is not an ideal treatment protocol. Although previous studies [18,25] have reported the effectiveness of this procedure, these infections were treated in acute type patients and the studies had small sample sizes. Debridement with the retention of the prosthesis was successful in 4 of the 22 patients examined [26]. The 4 patients who underwent initial surgical procedure by debridement with retention of the prosthesis all failed [13], which is similar to the outcome in the present study. Only 1 report described 1-stage exchange arthroplasty [27]; therefore, we cannot draw any conclusion from a case report. Although Garcia-Oltra et al. concluded that treatment with fluconazole and debridement or 2-stage replacement with a spacer was associated with a high failure rate [14], and resection arthroplasty and 2-stage revision were recommended to eradicate infection [7,13,16,21,26,28], the present study achieved an acceptable success rate (13/18). However, a surgeon should make the decision according to the condition of each patient. In high-risk group type C, consisting of individuals whose host risk factors were more than 2, all patients failed and had to undergo further debridement and prolonged use of antifungal agents.

Antibiotic-loaded bone cement spacers are now considered the criterion standard for the treatment of bacterial PJI [29]. However, whether this method is efficacious in the treatment of fungal PJI is controversial, especially for the type and dose of antifungal agents added to the bone cement. Amphotericin B has the advantage of being heat-stable and available in powder form, and has been reported to successfully treat fungal PJI [30]. However, it has also been reported to be difficult to elute from bone cement spacer [31]. In the present study, Vancomycin and Amphotericin B/Voriconazole were mixed into bone cement because of the high incidence of combined fungal and bacterial infection (33%) [7]. The minimum mixing ratio is 2 g of Vancomycin and 1 g of Amphotericin B in 120 g of bone cement (2.5%, Palacios MV+G), and the maximum mixing ratio is 8 g of Vancomycin, 2.5 g of Amphotericin B, and 1 g of Voriconazole in 80 g of bone cement (14.4%). In the success group, there were 5 joints that were mixed with antifungal agents in the spacer or their first spacer (5/12). In contrast, in the failure group, there were 2 joints that were mixed with antifungal agents in the spacer or their first spacer (3/5). (41.6% vs. 60%, $P=0.620$, Table 3). Mixing with antifungal agents may not help increase the success rate. No spacer fracture occurred prior to reimplantation, suggesting that the bone cement spacer mechanical character is not affected by Vancomycin, Amphotericin B, or Voriconazole.

System antifungal agent administration is of vital importance to controlling fungal infections. Amphotericin B and fluconazole were reported to be effective in a previous study [32,33]. However, the duration of antifungal agents has not been established. The Infectious Diseases Society of America (IDSA)

recommends treatment with Amphotericin B or fluconazole for at least 6 weeks after the removal of the arthroplasty in most patients with fungal PJI [23]. In the present study, most of the patients were administered intravenous fluconazole, Voriconazole, or Caspofungin for at least 6 weeks, with or without subsequent oral fluconazole treatment. The mean duration of oral fluconazole was 6.8 weeks (range, 0–20 weeks). In addition to fungal infection, 10 patients had infections mixed with other bacteria; therefore, sensitive antibiotics against bacteria were used. We do not recommend the use of other antibiotics in the absence of a specific bacterial infection. A long period of oral antifungal treatment has been recognized as an essential factor for the success of staged reimplantation after a fungal PJI [8]. However, the previous report compared 6 weeks with 3 months of antifungal treatment, in which antibiotic treatment does not influence the outcome after reimplantation. We suggest that 6 weeks parenteral antifungal agents are necessary, and 6 subsequent weeks of oral antifungal treatment is also important. Additionally, blood testing is required, and liver and kidney function should be regularly monitored, as 2 patients in our study had leukopenia after using of antifungal agents, and 1 of these patients also suffered renal insufficiency.

Several risk factors have been associated with fungal infection. Host factors include diabetes diseases, an immunosuppressive or immunodeficient status, rheumatoid arthritis, malignancy, tuberculosis, and renal transplantation or insufficiency [7,28,34]. In addition, immune and nutritional status can also determine the outcome [7]. However, in the present study, we did not find significant risk factors based on these. According to the univariate analysis, patients who have more than 1 risk factor of host and extremity were more likely to fail (15.4% vs. 40%, $P=0.53$, 69.2% vs. 100%, $P=0.278$) (Table 3). Although we did not find a statistically significant difference based in the present study, the higher failure rate in Host B/C and Extremity 2 indicated that worse host and extremity status may be associated with treatment failure, which needs further study and larger samples for confirmation.

The present study has several limitations. Firstly, the sample size was small, and only 17 patients (18 joints) were identified; thus, the strength of the data may be weakened. Secondly, because of a lack of guidelines concerning fungal diagnosis and treatment, different surgeons have different methods, especially in surgical treatment, antifungal regimens, antifungal agents loaded-in bone cement, and the interval between resection arthroplasty and reimplantation, we cannot provide a specific suggestion based on our research. Thirdly, due to the rarity of fungal infection, a randomized controlled study is difficult to perform, and the present retrospective study may have recall bias.

Conclusions

In conclusion, debridement with the retention of the prosthesis is not an ideal treatment protocol for fungal PJI, and 2-stage revision could be efficient. We suggest that 6 weeks of parenteral antifungal agents are necessary, followed by 6 weeks of oral antifungal treatment. We do not recommend performing the 2-stage revision in patients with more than 2 host risk factors.

References:

1. Vessely MB, Whaley AL, Harmsen WS et al: The Chitranjan Ranawat Award: Long-term survivorship and failure modes of 1000 cemented condylar total knee arthroplasties. *Clin Orthop Relat Res*, 2006; 452: 28–34
2. Ulrich SD, Seyler TM, Bennett D et al: Total hip arthroplasties: What are the reasons for revision? *Int Orthop*, 2008; 32(5): 597–604
3. Gwam CU, Mistry JB, Mohamed NS et al: Current epidemiology of revision total hip arthroplasty in the United States: National inpatient sample 2009 to 2013. *J Arthroplasty*, 2017; 32(7): 2088–92
4. Delanois RE, Mistry JB, Gwam CU et al: Current epidemiology of revision total knee arthroplasty in the United States. *J Arthroplasty*, 2017; 32(9): 2663–68
5. Pulido L, Ghanem E, Joshi A et al: Periprosthetic joint infection: The incidence, timing, and predisposing factors. *Clin Orthop Relat Res*, 2008; 466(7): 1710–15
6. Tsukayama DT, Estrada R, Gustilo RB: Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. *J Bone Joint Surg Am*, 1996; 78(4): 512–23
7. Azzam K, Parvizi J, Jungkind D et al: Microbiological, clinical, and surgical features of fungal prosthetic joint infections: A multi-institutional experience. *J Bone Joint Surg Am*, 2009; 91(Suppl. 6): 142–49
8. Phelan DM, Osmon DR, Keating MR, Hanssen AD: Delayed reimplantation arthroplasty for candidal prosthetic joint infection: A report of 4 cases and review of the literature. *Clin Infect Dis*, 2002; 34(7): 930–38
9. Chun KC, Kim KM, Chun CH: Infection following total knee arthroplasty. *Knee Surg Relat Res*, 2013; 25(3): 93–99
10. Kalore NV, Gioe TJ, Singh JA: Diagnosis and management of infected total knee arthroplasty. *Open Orthop J*, 2011; 5: 86–91
11. Wolff LH 3rd, Parvizi J, Trousdale RT et al: Results of treatment of infection in both knees after bilateral total knee arthroplasty. *J Bone Joint Surg Am*, 2003; 85-a(10): 1952–65
12. Meek RM, Masri BA, Dunlop D et al: Patient satisfaction and functional status after treatment of infection at the site of a total knee arthroplasty with use of the PROSTALAC articulating spacer. *J Bone Joint Surg Am*, 2003; 85-a(10): 1888–92
13. Hwang BH, Yoon JY, Nam CH et al: Fungal peri-prosthetic joint infection after primary total knee replacement. *J Bone Joint Surg Br*, 2012; 94(5): 656–59
14. Garcia-Oltra E, Garcia-Ramiro S, Martinez JC et al: [Prosthetic joint infection by *Candida* spp.]. *Rev Esp Quimioter*, 2011; 24(1): 37–41 [in Spanish]
15. McPherson EJ, Woodson C, Holtom P et al: Periprosthetic total hip infection: outcomes using a staging system. *Clin Orthop Relat Res*, 2002; (403): 8–15
16. Ueng SWN, Lee C-Y, Hu C-C et al: What is the success of treatment of hip and knee candidal periprosthetic joint infection? *Clin Orthop Relat Res*, 2013; 471(9): 3002–9
17. Cobo F, Rodriguez-Granger J, Lopez EM et al: *Candida*-induced prosthetic joint infection. A literature review including 72 cases and a case report. *Infect Dis*, 2017; 49(2): 81–94
18. Brooks DH, Puppato F: Successful salvage of a primary total knee arthroplasty infected with *Candida parapsilosis*. *J Arthroplasty*, 1998; 13(6): 707–12
19. Darouiche RO, Hamill RJ, Musher DM et al: Periprosthetic candidal infections following arthroplasty. *Rev Infect Dis*, 1989; 11(1): 89–96
20. Dutronc H, Dauchy FA, Cazanave C et al: *Candida* prosthetic infections: Case series and literature review. *Scand J Infect Dis*, 2010; 42(11–12): 890–95
21. Wang QJ, Shen H, Zhang XL et al: Staged reimplantation for the treatment of fungal peri-prosthetic joint infection following primary total knee arthroplasty. *Orthop Traumatol Surg Res*, 2015; 101(2): 151–56
22. Parvizi J, Zmistowski B, Berbari EF et al: New definition for periprosthetic joint infection: from the Workgroup of the Musculoskeletal Infection Society. *Clin Orthop Relat Res*, 2011; 469(11): 2992–94
23. Osmon DR, Berbari EF, Berendt AR et al: Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*, 2013; 56(1): e1–e25
24. Atkins BL, Athanasou N, Deeks JJ et al: Prospective evaluation of criteria for microbiological diagnosis of prosthetic-joint infection at revision arthroplasty. The OSIRIS Collaborative Study Group. *J Clin Microbiol*, 1998; 36(10): 2932–39
25. Merrer J, Dupont B, Nieszkowska A et al: *Candida albicans* prosthetic arthritis treated with fluconazole alone. *J Infect*, 2001; 42(3): 208–9
26. Kuiper JW, van den Bekerom MP, van der Stappen J et al: 2-stage revision recommended for treatment of fungal hip and knee prosthetic joint infections. *Acta Orthop*, 2013; 84(6): 517–23
27. Selmon GP, Slater RN, Shepperd JA, Wright EP: Successful 1-stage exchange total knee arthroplasty for fungal infection. *J Arthroplasty*, 1998; 13(1): 114–15
28. Anagnostakos K, Kelm J, Schmitt E, Jung J: Fungal periprosthetic hip and knee joint infections clinical experience with a 2-stage treatment protocol. *J Arthroplasty*, 2012; 27(2): 293–98
29. Cui Q, Mihalko WM, Shields JS et al: Antibiotic-impregnated cement spacers for the treatment of infection associated with total hip or knee arthroplasty. *J Bone Joint Surg Am*, 2007; 89(4): 871–82
30. Wu MH, Hsu KY: Candidal arthritis in revision knee arthroplasty successfully treated with sequential parenteral-oral fluconazole and amphotericin B-loaded cement spacer. *Knee Surg Sports Traumatol Arthrosc*, 2011; 19(2): 273–76
31. Goss B, Lutton C, Weinrauch P et al: Elution and mechanical properties of antifungal bone cement. *J Arthroplasty*, 2007; 22(6): 902–8
32. Pappas PG, Kauffman CA, Andes D et al: Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*, 2009; 48(5): 503–35
33. Austen S, van der Weegen W, Verduin CM et al: *Coccidioidomycosis* infection of a total knee arthroplasty in a nonendemic region. *J Arthroplasty*, 2013; 28(2): 375.e13–15
34. Kelesidis T, Tsiodras S: *Candida albicans* prosthetic hip infection in elderly patients: is fluconazole monotherapy an option? *Scand J Infect Dis*, 2010; 42(1): 12–21

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conflict of interest

None.