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Microbiological, Clinical, and Surgical Features of Fungal Prosthetic Joint Infections: A Multi-Institutional Experience

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Introduction

Periprosthetic joint infection is one of the most dreaded and complex complications of total joint arthroplasty. Periprosthetic joint infection is now the major cause of failure following total knee arthroplasty[1] and the third most common cause of failure following total hip arthroplasty[2]. It is estimated that the prevalence of periprosthetic joint infection may be on the rise[3]. A wide variety of pathogens are known to cause periprosthetic joint infection, with the majority of infections being caused by gram-positive bacteria, especially staphylococcal species[4,5]. The treatment of a confirmed periprosthetic joint infection often includes the need for surgical intervention, and two-stage exchange arthroplasty is the most common mode of surgical treatment in North America. Two-stage exchange arthroplasty relies on removal of all foreign material and insertion of an antibiotic-impregnated cement spacer for the purpose of delivering high doses of antibiotics locally in the interval of time between the resection arthroplasty and subsequent reimplantation.

Periprosthetic infection with fungi, although rare, represents a diagnostic and therapeutic challenge to which clear guidelines have not yet been established. It is not known if the protocol for treatment of a bacterial periprosthetic joint infection can also be applied in the same manner to fungal infections. Patients with fungal periprosthetic joint infection are believed to be a different type of host with decreased cellular immunity, mostly due to an underlying cause of immunosuppression, such as malignant disease, drug therapies (antineoplastic agents, corticosteroids, or immunosuppressive drugs), overuse or inappropriate use of antibiotics, and indwelling catheters (urinary or parenteral hyperalimentation). Other factors, such as diabetes, tuberculosis, intravenous drug use, and acquired immunosuppressive disease, are associated with an increased frequency of mycotic infection[6]. The lack of reliable antifungal medications for systemic and, in particular, local delivery poses a real challenge in pathogen-directed treatment. The literature contains few reports of fungal periprosthetic joint infection. In fact, our search of the entire English literature revealed a total of forty-six patients[7-40]. The vast majority of those infections were caused by Candida species. Previous case reports present a wide variety of treatment methods, both surgical and medical, as well as variable outcomes. Based on the very small number of patients in each report, it is difficult to draw firm conclusions regarding the outcome of treatment for this challenging problem. Further, the surgical treatment varies considerably for these patients, making interpretation of the presented data difficult and not directly comparable.

The purpose of this multicenter study was therefore to investigate the issues surrounding this rare condition with respect to patient characteristics and the currently implemented therapeutic strategies and their effectiveness. In particular, this study sought to determine the efficacy of two-stage exchange arthroplasty in the treatment of these complex infections.

Materials and Methods

We performed a review of joint arthroplasty databases in six centers to identify patients who were diagnosed with a periprosthetic fungal infection. Patients were diagnosed with fungal periprosthetic joint infection according to a positive preoperative aspiration culture and/or a positive intraoperative culture. We collected patient-specific information, including demographics, body mass index, smoking habits, comorbidities (especially immunity-impairing risk factors such as diabetes mellitus, corticosteroid therapy, malignant disease, and organ transplantation), and prolonged antibiotic treatment. Medical records were reviewed at each center to identify the clinical, laboratory, and operative characteristics of patients with infection as well as the treatment protocols that had been used. Patients were followed radiographically for at least two years or until recurrence of the infection. The average period of follow-up for patients who remained free of infection was forty-five months (range, twenty-four months to eleven years). Institutional review board approval was obtained in each center prior to initiating the study.

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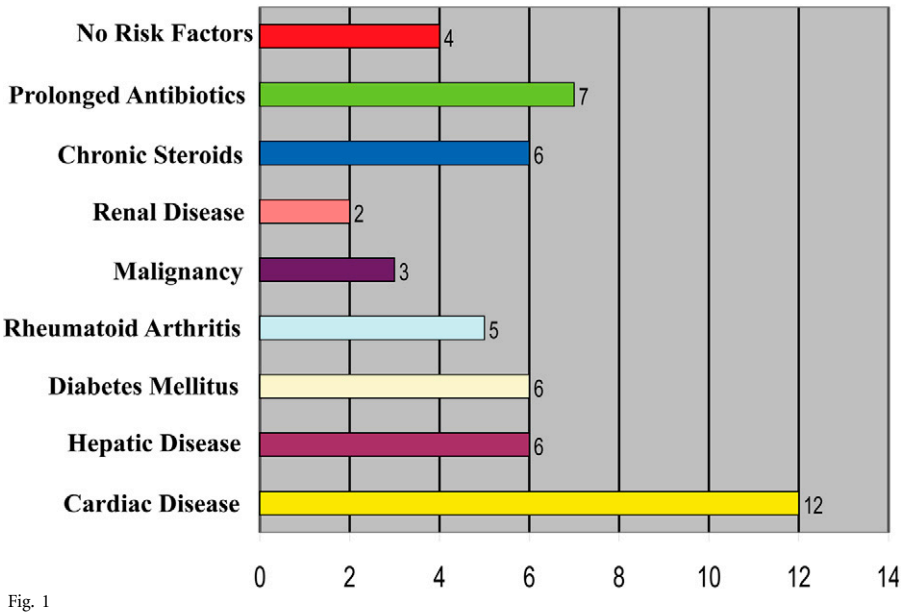

Fig. 1

Potential immunity-impairing risk factors in the study population. (Note: the numbers do not equal the number of patients due to overlap.)

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Results

From 1999 to 2006, a total of thirty-one patients with fungal infection about a total hip or knee prosthesis were identified. There were seventeen women and fourteen men with an average age of sixty-four years (range, thirty-six to eighty-six years) at the time of diagnosis, and they had an average body mass index of 29.1 kg/m^2 (range, 17 to 48.6 kg/m^2). Infection occurred after knee arthroplasty in seventeen patients and after hip arthroplasty in fourteen patients. Twenty-seven patients had one or more underlying systemic illnesses (Fig. 1), including cardiac disease in twelve patients, chronic liver disease in six patients, diabetes mellitus in six patients, rheumatoid arthritis in five patients, malignant disease in three patients, and chronic renal failure in two patients. Six patients were receiving systemic corticosteroid therapy at the time of presentation. Seven patients received a prolonged course of antibiotics prior to the development of the fungal infection. In four patients, no risk factors of impaired immunity could be identified. Two of those four patients developed the infection after multiple (more than five) revision surgeries. Another patient had a complicated history of multiple gunshot wounds to the extremity with the infected joint.

The interval from the index surgery to the diagnosis of infection averaged twenty-five months (range, one month to twelve years). Fungal periprosthetic infection occurred after a primary arthroplasty in eleven patients and after a revision arthroplasty in the remaining twenty patients. All patients presented with symptoms and signs of chronic infection, which included chronic pain and swelling. None of the patients had systemic symptoms including fever. Loosening of the implant was detected radiographically in seven patients, with extensive femoral osteolysis detected in one patient. The average erythrocyte sedimentation rate and C-reactive protein level were 54 mm/hr (range, 12 to 104 mm/hr) and 17.5 mg/L (range, 0.6 to 73.9 mg/L), respectively. In eleven patients, preoperative aspiration and examination of the joint fluid revealed an average white blood-cell count of 8761 cells/μL (8.76×10^9/L) (range, 440 to 26,700 cells/μL [0.4 to 26.7 $\times$ 10^9/L]) with an average neutrophil differential of 76% (range, 19% to 94%).

Candida species was the causative pathogen in the majority of the patients. *Candida albicans* was grown in cultures of specimens from twenty patients; *Candida parapsilosis,* in four patients; both fungi in three patients; and *Candida glabrata,* in one patient. Non-Candida species were isolated in three patients and included Aspergillus in one patient, *Rhodotorula minuta* in another patient, and Aureobasidium in the third patient. An intraoperative Gram stain did not reveal organisms in any of the patients. A coexisting bacterial infection was detected in five patients; the organisms included coagulase-negative Staphylococci in three patients, vancomycin-resistant enterococci in one patient, and *Staphylococcus aureus* in another patient.

Irrigation and débridement was the initial surgical treatment in seven patients, none of whom had resolution of the infection. Five of these patients required removal of the prosthesis to eradicate the infection. Due to the extent of bone loss, which prohibited further reconstruction, the infection was suppressed with oral fluconazole in the remaining two patients. Meanwhile, twenty-four patients were initially man-

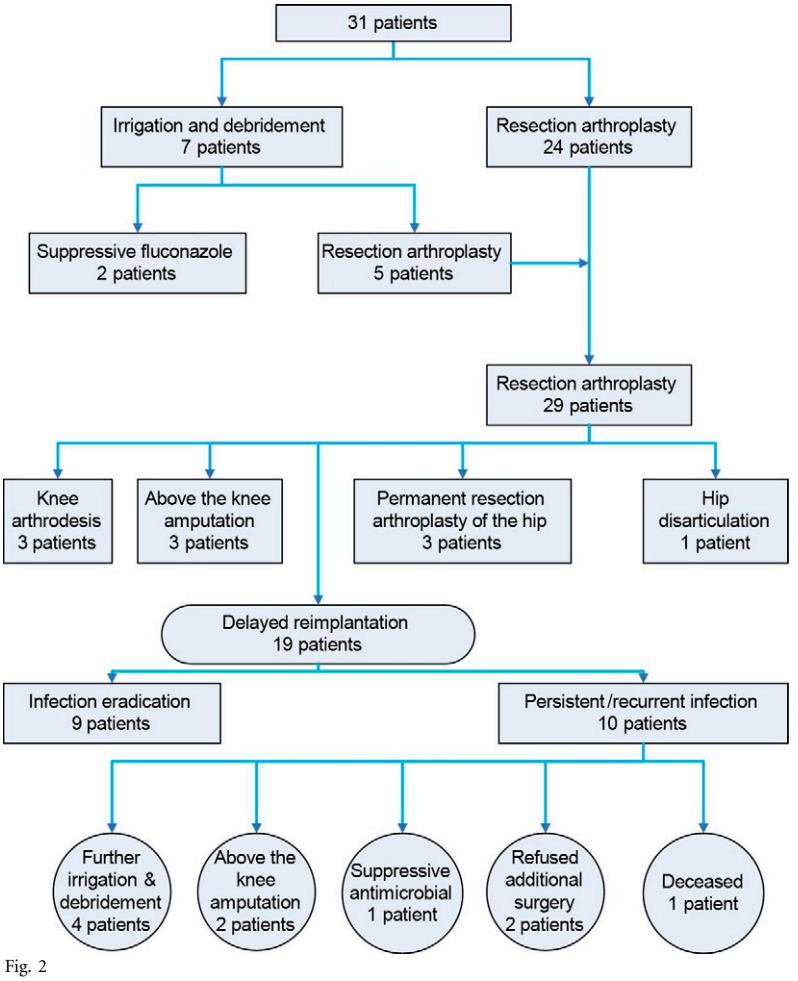

Fig. 2

A flowchart outlines the surgical treatment of fungal prosthetic joint infection in thirty-one patients from six different centers between 1999 and 2006.

aged with resection of the components. Thus a total of twenty-nine patients required resection arthroplasty to control the infection (Fig. 2). Implants and cement, whenever present, were removed, and a thorough débridement of devitalized tissues was carried out in all patients. For all patients, a spacer was inserted that contained the antibiotics tobramycin and vancomycin; in five patients, the spacer also contained the antifungal medication amphotericin.

Of the twenty-nine patients who underwent resection arthroplasty and spacer insertion, delayed reimplantation was performed in nineteen at an average of seven months (range, two to fourteen months) after the resection arthroplasty. Multiple intraoperative cultures were obtained at the time of reimplantation, and these cultures were negative in all nineteen patients. Ten of the nineteen patients showed signs of persistent or recurrent infection after reimplantation. Four of these ten underwent further irrigation and débridement; the cultures that were obtained during that procedure did not demonstrate any fungal growth and these patients were free of infection at the time of the latest follow-up as of the time of writing. Two of the ten patients underwent above-the-knee amputation. Of the remaining four of these ten patients, one patient died due to uncontrolled sepsis that resulted in multiple organ system failure, another patient was managed on long-term suppressive antimicrobial therapy, and two patients refused additional surgery. As a result of uncontrolled infection, reimplantation was never performed in ten of the twenty-nine patients. Multiple operative débridement and spacer exchange procedures were performed in an attempt to control the infection. Nevertheless, the final outcome of these ten patients was above-the-knee amputation in three patients, knee arthrodesis in three patients, permanent resection arthroplasty of the hip in three patients, and hip disarticulation in one patient (Fig. 2).

Following the initial surgical treatment (resection arthroplasty or débridement), all thirty-one patients were managed with six weeks of intravenous antifungal agents. Fluconazole was used in twenty-three patients, with an initial dose of 800 mg/day that was gradually tapered to 400 mg/day. Three patients were treated with caspofungin (50 to 75 mg/day) in addition to fluconazole. Amphotericin B, 3 mg/kg/day, was used in five patients. Antifungal susceptibility testing

TABLE I Reports of Fungal Prosthetic Joint Infections*

No.	Study	Organism	Joint	Treatment	Outcome	Follow-up
1	MacGregor et al.[26] (1979)	*Candida parapsilosis*	Knee	Resection arthroplasty	Arthrodesis	1 yr
2,3	Goodman et al.[17] (1983)	*Candida tropicalis*	Knee	Resection arthroplasty	Arthrodesis	1 yr
		Candida glabrata	Hip	Resection arthroplasty	Resection arthroplasty	1 yr
4	Younkin et al.[40] (1984)	*Candida parapsilosis*	Hip	Resection arthroplasty	Resection arthroplasty	2 yr
5	Koch[20] (1988)	*Candida albicans*	Knee	Resection arthroplasty	Arthrodesis	21 mo
6	Iskander and Kahn[19] (1988)	*Candida albicans*	Knee	Resection arthroplasty	Arthrodesis	N/A
7	Levine et al.[25] (1988)	*Candida albicans*	Knee	Resection arthroplasty	Arthrodesis	2 yr
8,9	Lambertus et al.[21] (1988)	*Candida tropicalis*	Hip	Resection arthroplasty	Resection arthroplasty	2 yr
		Candida tropicalis	Knee	Resection arthroplasty	Resection arthroplasty	14 mo
10-13	Darouiche et al.[13] (1989)	*Candida albicans*	Hip (2 cases)	Resection arthroplasty	Resection arthroplasty	7 mo
		Candida albicans	Knee	Resection arthroplasty	Resection arthroplasty	6 wk
		Candida tropicalis	Hip	Resection arthroplasty	Resection arthroplasty	3 yr
14,15	Evans and Nelson[14] (1990)	*Candida albicans*	Hip (2 cases)	Resection arthroplasty	Resection arthroplasty	3.5 yr
16	Paul et al.[30] (1992)	*Candida parapsilosis*	Knee	Resection arthroplasty	Arthrodesis	2 yr
17	Austin et al.[8] (1992)	*Aspergillus fumigatus*	Knee	Resection arthroplasty	Resection arthroplasty	12 wk
18	Tunkel et al.[35] (1993)	*Candida parapsilosis*	Knee	Antifungal therapy	Amputation	N/A
19	White and Goetz[37] (1995)	*Candida parapsilosis*	Knee	Resection arthroplasty	Resection arthroplasty	2 yr
20-22	Cardinal et al.[11] (1996)	*Candida albicans*	Hip (3 cases)	Resection arthroplasty	Resection arthroplasty	6 mo to 1 yr
23	Hennessy[18] (1996)	*Candida parapsilosis*	Knee	Two-stage exchange	Infection cleared	2 yr
24	Nayeri et al.[29] (1997)	*Candida glabrata*	Hip	Resection arthroplasty	Resection arthroplasty	2 yr
25	Cushing and Fulgenzi[12] (1997)	*Candida parapsilosis*	Knee	Antifungal therapy	Infection suppression	1 yr
26	Fukasawa and Shirakura[15] (1997)	*Candida parapsilosis*	Knee	Débridement	Infection cleared	2 yr
27	Simonian et al.[34] (1997)	*Candida albicans*	Knee	Débridement	Infection cleared	6 yr
28	Selmon et al.[33] (1998)	*Candida glabrata*	Knee	One-stage exchange	Infection cleared	4 yr
29	Brooks and Pupparo[10] (1998)	*Candida parapsilosis*	Knee	Débridement	Infection cleared	2 yr
30	Wada et al.[36] 1998	*Candida parapsilosis*	Knee	Débridement	Infection cleared	3 yr
31	Baumann et al.[9] (2001)	*Aspergillus fumigatus*	Knee	Resection arthroplasty	Resection arthroplasty	5 yr
32	Ramamohan et al.[32] (2001)	*(Candida albicans)*	Hip	Resection arthroplasty	Resection arthroplasty	2 yr
33	Yang et al.[39] (2001)	*Candida parapsilosis*	Knee	Two-stage exchange	Infection cleared	4 yr
34	Merrer et al.[28] (2001)	*Candida albicans*	Hip	Antifungal therapy	Infection cleared	11 mo
35	Açikgöz et al.[7] (2002)	*Candida glabrata*	Knee	Resection arthroplasty	Arthrodesis	30 wk
36	Marra et al.[27] (2001)	*Candida albicans*	Hip	Articulating spacer	Resection arthroplasty	N/A
37-40	Phelan et al.[31] (2002)	*Candida albicans*	Hips (3)	Two-stage exchange	Infection cleared	4.3 yr
		Candida albicans	Knee (1)	Two-stage exchange	Infection cleared	4.3 yr
41	Wyman et al.[38] (2002)	*Candida tropicalis*	Knee	Two-stage exchange	Infection cleared	3 yr
42	Cutrona et al.[41] (2002)	*Rhodotorula minuta*	Hip	Two-stage exchange	Infection cleared	N/A
43	Lerch et al.[24] (2003)	*Candida albicans*	Knee	Resection arthroplasty	Arthrodesis	2 yr
44	Langer et al.[22] (2003)	*Aspergillus niger*	Knee	Antifungal therapy	Infection cleared	1 yr
45	Lazzarini et al.[23] (2004)	*Candida albicans*	Hip	Resection arthroplasty	Resection arthroplasty	4 yr
46	Gaston and Ogden[16] (2004)	*Candida glabrata*	Knee	Resection arthroplasty	Amputation	6 mo

*N/A = not available.

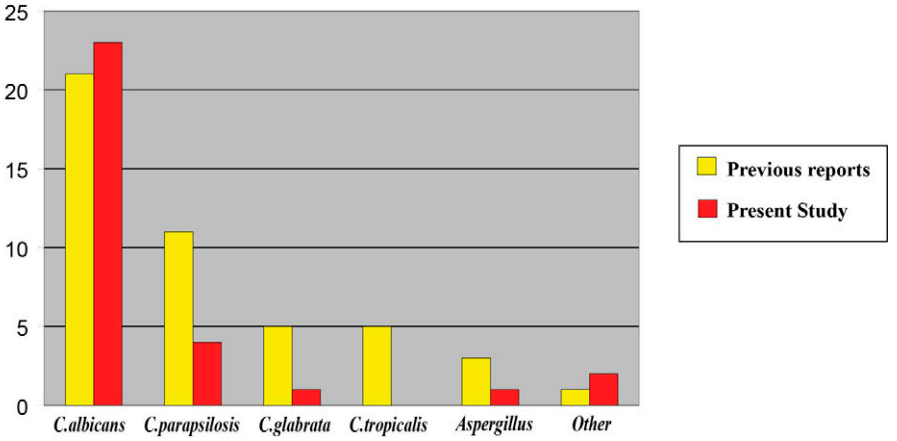

Fig. 3

Number of fungal periprosthetic infections reported so far according to our literature search. C. = Candida.

showed a sensitivity to amphotericin with average minimal inhibitory concentration values ranging from 0.5 to 1 μg/mL. Two patients experienced side effects of amphotericin treatment, namely, an elevated serum creatinine level in one patient and rigors and nausea in another. Following reimplantation, oral fluconazole was routinely prescribed for six months with regular monitoring of liver function tests.

Discussion

Periprosthetic infection caused by fungal pathogens is rare. Little is known about the prevalence of those infections, the accuracy of the currently used diagnostic modalities, or the most effective treatment protocol. We found a total of forty-six cases of reported fungal periprosthetic joint infection[7-40] after searching the English-language literature from 1979 to 2008 (Table I). Most of those infections were caused by Candida species. *Candida albicans* was the causative organism in twenty-one of forty-six cases[11,13,14,19,20,23-25,27,28,31,34]. *Candida parapsilosis* was the second leading cause of fungal periprosthetic joint infection and was isolated in eleven cases[10,12,15,18,26,30,35-37,39,40], *Candida glabrata* was isolated from five cases[7,16,17,29,32,33], and *Candida tropicalis* from five cases[13,17,21,38]. *Rhodotorula minuta* was reported as the cause of a periprosthetic infection in one case report[41]. In the remaining three reported cases, Aspergillus species (*Aspergillus fumigatus* and *Aspergillus niger*) was the causative pathogen[8,9,22]. A similar organism profile was noted in the present report (Fig. 3).

It seems that the most important virulence factor for fungi, especially *Candida albicans,* in the pathogenesis of periprosthetic infection is biofilm formation. Biofilm confers resistance to antifungal agents. It has been shown that *Candida albicans* produces larger and more complex biofilms than other Candida species do[42,43]. Host factors appear to play an important role in development of invasive fungal infections. At least one underlying chronic medical condition was identified in twenty-seven of the thirty-one patients in this series. However, among the previously reported cases of fungal prosthetic infections, roughly half of the patients had no obvious immunity-impairing risk factors[39]. Other important predisposing factors include multiple revision surgeries and complex reconstructions, the effect of which could be explained in part by the role of prolonged hospitalizations, which have also been identified as a risk factor for the development of candidemia[6].

The diagnosis of a fungal periprosthetic joint infection can be quite challenging. The mere demonstration of fungi in tissue or fluid samples obtained with aspiration of a prosthetic joint can be indicative of a true infection or fungal colonization. The dilemma is more pronounced when the culture demonstrates fungal organisms in association with an established bacterial infection. In all of our patients, serological values and joint-fluid cell counts could not distinguish a fungal infection from a bacterial infection with fungal contamination. The identification of fungal pathogens in synovial fluid or purulent secretions on Gram stains is rare. Examination of tissue samples should be done with use of special stains and cultures. The cultures should not be considered negative for growth until four weeks after incubation. In one study[7], fungi were not detected in any tissue sample until scrapings from the surface of the explanted prosthesis were examined. In other studies[24,30], the diagnosis of candidal prosthetic infection has been confirmed with direct histologic evidence of fungi in retrieved osseous specimens. Several investigators[10,32,33,36] have stressed the importance of repeating fluid cultures and obtaining multiple positive tissue cultures before a diagnosis of fungal periprosthetic joint infection is made.

This study showed that irrigation and débridement alone, as was undertaken for a subset of the patients, failed to control the infection. Wada et al.[36] successfully treated a *Candida parapsilosis* infection of the knee with débridement and a regimen of oral fluconazole sodium (400 mg/day) for six months. Only a few other reports[10,15,34] have shown successful treatment of fungal periprosthetic joint infection with débridement alone, which suggests that resection arthroplasty,

in accordance with the guidelines of the Infectious Diseases Society of America (IDSA)[44], should be undertaken when a fungal infection is confirmed. Additionally, débridement with retention of the prosthesis is unlikely to result in resolution of the fungal infection, as fungal infection almost always presents as a chronic infection in an immunocompromised host, both of which are recognized causes of failure of débridement alone[45,46]. Two-stage exchange arthroplasty failed to control the infection in ten of nineteen patients in this cohort. Phelan et al.[31] reported a recurrence rate of 20% after two-stage reimplantation for the treatment of candidal periprosthetic joint infection. When the results of this series are incorporated and viewed as a whole, it seems possible that the risk of relapse following delayed reimplantation arthroplasty for treatment of a fungal periprosthetic joint infection could be as high as 25%. One-stage exchange arthroplasty for fungal periprosthetic infection has been successful in only one reported case[33].

To date, there is no general consensus regarding the type and dose of antifungal agents that can be used locally, mixed with cement, or administered systemically to treat this challenging condition. Because of the fact that it is heat stable, broad spectrum, and available in sterile powder form, amphotericin B appears to be an ideal agent to be mixed with cement; however, a previous study showed no elution of amphotericin B from Simplex bone cement (Stryker Orthopaedics, Mahwah, New Jersey) after one week in vitro[47]. Another study showed undetectable serum concentrations of amphotericin B at fifty hours in vivo when mixed with Palacos bone cement (Biomet, Warsaw, Indiana)[27]. This means that an effective method of local delivery of an antifungal agent remains undetermined.

The drugs of choice for systemic administration in patients who are infected with Candida species are amphotericin B and fluconazole[44]. Drug therapy alone will only suppress clinical symptoms of infection at the expense of potential toxic side effects. Treatment with antifungal agents has been reported to be successful without surgical intervention in two previous reports[12,28], but resistance of Candida species to azole drugs has been reported[33]. In the current series, resistance to fluconazole was noted among *Candida glabrata* infections. Thus, selecting the appropriate antifungal treatment requires antifungal susceptibility testing and a multiteam approach involving infectious disease specialists, clinical pharmacologists, and the treating orthopaedic surgeon. Although the exact duration of therapy is not agreed upon, it seems that, on the basis of previous reports, a minimum of one year is necessary to ensure resolution of the infection[12,15,35]. The IDSA guidelines for the duration of treatment with antifungal agents in the treatment of native joint arthritis are six to twelve months (Grade-BIII recommendation)[44,48].

In summary, the findings of this first large-scale multicenter study on prosthetic joint infections caused by fungal pathogens support the notion that proper tissue débridement and removal of the arthroplasty components may be the appropriate surgical treatment for the majority of patients. Débridement and retention of components has a limited role and should be reserved for the healthy host with excellent soft tissues and a truly acute infection. Two-stage exchange arthroplasty is the treatment of choice. It is important to ensure that antibacterial drugs are also added to the cement spacer to prevent superinfection or to treat coexistent bacterial pathogens. The appropriate choice of antifungal agent for addition to the cement spacer remains controversial. At present, the only available agent is amphotericin. The determination of the appropriate dose of this drug depends on the type of fungal infection, the sensitivity of the pathogen to this drug, and the preexisting comorbidities of the host. Systemic antifungal therapy should then be initiated on the basis of the results of fungal susceptibility testing, and this therapy should be continued until resolution of the infection can be established on the basis of clinical and serological evaluation. Prior to reimplantation, repeat joint aspirations should be performed in all patients. According to the guidelines issued by the IDSA[48], antifungal drugs should be administered for a total duration of six to twelve months. All efforts should be made to optimize the host prior to reimplantation. The nutritional status of the host should be evaluated and, when necessary, corrected. Reimplantation should therefore be deferred until immunity-impairing risk factors have been reversed or minimized. ■

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