# 2-stage revision recommended for treatment of fungal hip and knee prosthetic joint infections

## An analysis of 164 patients, 156 from the literature and 8 own cases

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**Background and purpose** **Fungal prosthetic joint infections are rare and difficult to treat. This systematic review was conducted to determine outcome and to give treatment recommendations.**

**Patients and methods** **After an extensive search of the literature, 164 patients treated for fungal hip or knee prosthetic joint infection (PJI) were reviewed. This included 8 patients from our own institutions.**

**Results** **Most patients presented with pain (78%) and swelling (65%). In 68% of the patients, 1 or more risk factors for fungal PJI were found. In 51% of the patients, radiographs showed signs of loosening of the arthroplasty. Candida species were cultured from most patients (88%). In 21% of all patients, fungal culture results were first considered to be contamination. There was co-infection with bacteria in 33% of the patients. For outcome analysis, 119 patients had an adequate follow-up of at least 2 years. Staged revision was the treatment performed most often, with the highest success rate (85%).**

**Interpretation** **Fungal PJI resembles chronic bacterial PJI. For diagnosis, multiple samples and prolonged culturing are essential. Fungal species should be considered to be pathogens. Co-infection with bacteria should be treated with additional antibacterial agents.**

**We found no evidence that 1-stage revision, debridement, antibiotics, irrigation, and retention (DAIR) or antifungal therapy without surgical treatment adequately controls fungal PJI. Thus, staged revision should be the standard treatment for fungal PJI. After resection of the prosthesis, we recommend systemic antifungal treatment for at least 6 weeks—and until there are no clinical signs of infection and blood infection markers have normalized. Then reimplantation can be performed.**

Prosthetic joint infection (PJI) is the most debilitating and expensive complication following arthroplasty (Bozic and Ries 2005). A nationwide study performed in the USA showed an infection burden of 1.23% for THA and 1.21% for TKA, with an almost 2-fold increase between 1990 and 2004 (Kurtz et al. 2008).

Fungal PJI is uncommon, and occurs in approximately 1% of all PJIs (Phelan et al. 2002, Azzam et al. 2009). There are few reports in the literature and most of them have included only a small number of patients (Azzam et al. 2009, Dutronc et al. 2010, Anagnostakos et al. 2012, Hwang et al. 2012). Most fungal PJIs are caused by *Candida albicans* and *Candida parapsilosis* (Azzam et al. 2009). Extensive comorbidity and decreased immunity are considered risk factors for fungal infections (Phelan et al. 2002, Azzam et al. 2009). The surgical treatment options are similar to those for bacterial PJIs (Azzam et al. 2009). The Infectious Diseases Society of America recommends removal of the arthroplasty in most patients, with therapy for at least 6 weeks with fluconazole or amphotericin B (Osmon et al. 2013). If removal of the arthroplasty is not an option, for instance due to the poor health of the patient, chronic suppression with fluconazole is recommended (Pappas et al. 2009).

This review covers 156 previously reported cases of fungal hip and knee PJI and 8 patients from our own institutions. We have analyzed treatment options and outcome.

## Patients and methods

The following online databases were searched: Medline (period 1966 to July 2012), Cochrane Clinical Trial Register


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(1988 to July 2012), and Embase (January 1988 to July 2012). The search was performed independently by 2 reviewers (JK and SC). Disagreement was resolved by consensus and third party adjudication.

Using the search terms "prosthesis implantation[Mesh]" AND "candida[Mesh]", "(candida OR fungal) AND (((hip OR knee) AND prosthesis) OR arthroplasty)", "(candida OR fungal) AND (prosthesis OR arthroplasty) NOT medline[sb]", we initially found 1,411 articles. The titles, abstracts, and keywords of these papers were reviewed and the full publications were retrieved if there was insufficient information to determine appropriateness for inclusion. All publications considered relevant were read completely. In addition, reference lists of publications included were checked for articles that had been missed initially. Articles that were not in English were included if translation was possible.

We also retrospectively studied patient files from all patients who had been treated for fungal PJI at our institutions between 2003 and 2011.

Data collected from all the articles included and from patients from our own institutions included: age, sex, affected joint, primary or revision surgery, comorbidity, preoperative diagnosis, symptoms, duration of symptoms, interval between primary surgery and onset of symptoms of infection, species isolated, origin of culture samples (i.e. aspiration, intraoperative, other), other microorganisms cultured, fungal culture considered irrelevant (yes or no), C-reactive protein (CRP, mg/L) and erythrocyte sedimentation rate (ESR, mm/h) at presentation, radiographic findings, local and systemic antimicrobial therapy, duration of antimicrobial therapy, type of surgical treatment, time from resection to reimplantation, outcome, and duration of follow-up.

### *Definitions*

Risk factor status was based on risk factors previously mentioned by others: an immunosuppressive or immunodeficient status, diabetes mellitus, rheumatoid arthritis, a history of renal insufficiency, malignancy or previous PJI (Azzam et al. 2009, Dutronc et al. 2010, Kelesidis and Tsiodras 2010, Garcia-Oltra et al. 2011, Wu and Hsu 2011, Anagnostakos et al. 2012, Chiu et al. 2013).

Since criteria used to define infection were not always clearly noted by other authors, we decided to consider all fungal infections described in the individual studies as definite fungal infections.

Cure of fungal PJI was defined as good clinical function and absence of infectious signs and symptoms, with the arthroplasty present (either after staged revision or after debridement), without the use of chronic antifungal or antibacterial therapy and with a follow-up of at least 2 years.

Baseline data, such as patient characteristics and culture results, are not only described for patients with a follow-up of at least 2 years, but for all the patients included.

### *Studies included*

68 studies describing fungal hip and knee PJI were found. 2 of 10 patients were excluded in a group of fungal PJI patients because the infected joint was unclear (Garcia-Oltra et al. 2011). From 1 study, 4 of 6 patients were excluded, as fungal native joint infection before arthroplasty was proven or strongly suspected (Kuberski et al. 2011). 1 article described 10 patients, 6 of which had already been reported (Phelan et al. 2002). In total, 64 studies were included, describing 156 patients (Table 1, see supplementary data). We included 8 more patients from our own institutions (Table 2, see supplementary data), giving a total of 164 patients.

## Results

### *Patient characteristics*

164 patients were included (63% female). 94 patients had a fungal infection of a knee arthroplasty and 70 had a fungal infection of a hip arthroplasty. Infection occurred after primary arthroplasty in 68 patients, after revision arthroplasty in 53 patients, and in 43 patients primary or revision arthroplasty was not specified. In 17 patients, the duration of follow-up was not reported, and in 32 patients follow-up was less than 2 years, leaving 119 patients with a follow-up of at least 2 years (Figure).

Possible risk factors predisposing for PJI were accurately described in 148 patients: 101 patients had 1 or more risk factors for PJI (68%) (Table 3).

### *Clinical features and diagnosis*

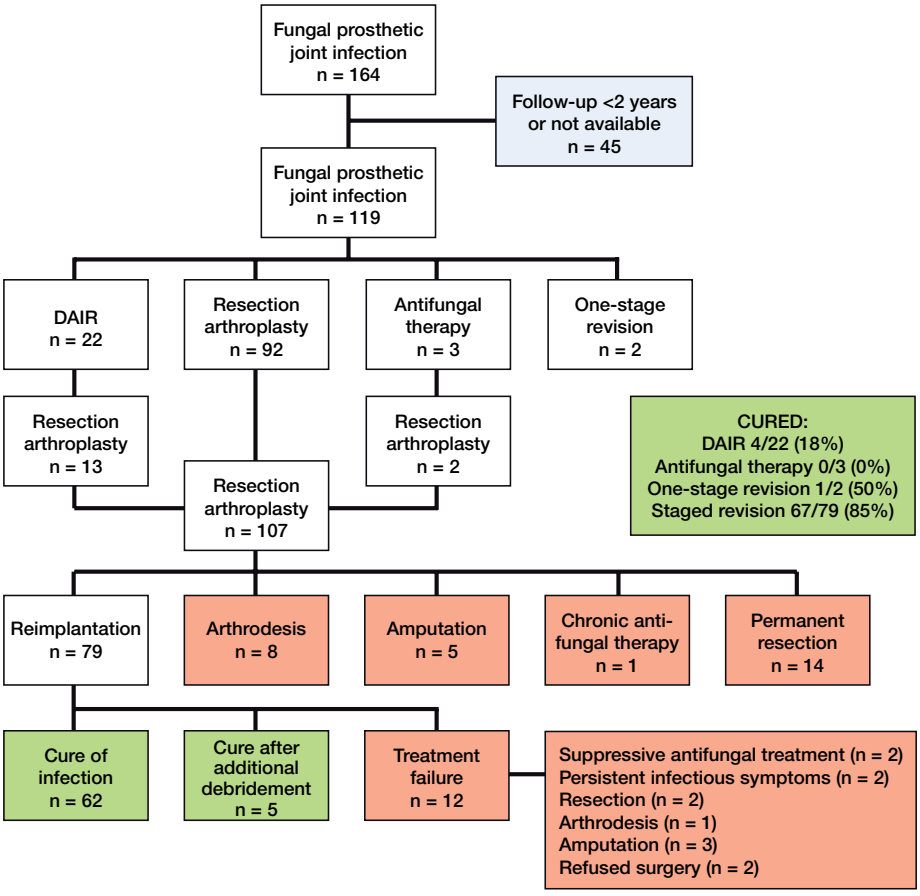
Clinical symptoms were described for 147 patients. Most patients presented with symptoms of chronic infection such as pain (78%) and swelling (65%). Other symptoms included warmth (18%), limited range of motion (10%), redness (8%), and fever (7%). Wound drainage and sinus tract were described in 4% and 9% of patients, respectively.

The mean duration from last performed arthroplasty (primary or revision) to diagnosis of fungal PJI was 27 months (range 2 weeks to 22 years). 29% of the patients had an infection-free period of at least 2 years after the index surgery.

Plain radiography results were described in 118 patients. In 60 patients, signs of loosening of the prosthesis were seen ("loosening", "lucency", and "osteolysis").

Blood levels of CRP (in mg/L) and ESR (in mm/h) were available in 91 and 101 patients, respectively. In 4 reports, the unit of CRP blood levels was not mentioned, and these were left out (some authors reported in mg/L and others in mg/dL). Mean CRP levels at presentation were 44 (0.9–280) mg/L; mean ESR was 53 (7–141) mm/h.

The final diagnosis was always based on culture results, from aspiration fluid alone (n = 32), intraoperative specimens alone (n = 45), or aspiration and intraoperative specimens combined (n = 32). In 3 patients, the microorganism was




Flow chart describing the outcome of surgical treatment in 119 patients with fungal hip or knee PJI and with an adequate follow-up.

**Table 3. Numbers of patients with risk factors for fungal PJI, described in 148 patients with fungal PJI**

| Risk factor | No. of patients (of 148 in total) |
|---|---|
| None | 47 |
| Diabetes mellitus | 38 |
| Malignancy | 10 |
| Renal disease | 8 |
| Rheumatoid arthritis | 20 |
| Immunosuppression | 23 |
| Prior PJI | 20 |

detected intraoperatively and with another method (1 blood culture, 1 wound drainage, 1 sinus tract).

For 51% of the patients (n = 84), it was reported whether or not the initial fungal cultures were considered to be contaminants. For 18 patients (21%), the fungal cultures were initially considered contamination.

## *Microbiology*

Most fungal PJIs were caused by candida species (n = 145; 88%), the commonest being *Candida albicans* (n = 78; 48%). Other candida species were *C. parapsilosis* (n = 40), *C. glabrata* (n = 14), *C. tropicalis* (n = 6), *C. pelliculosa* (n = 3), *C. lipolytica, C. guillermondii, C. famata,* and *C. lusitaniae* (all n = 1). 5 patients had polyfungal infections, all caused by candida. Other fungal species were found in 24 patients and included species such as *Aspergillus fumigatus, Pichia anomala,* and *Rhodotorula minuta.*

In 54 patients, bacteria were also cultured (33%). Coagulase-negative *Staphylococcus* was cultured in 26 patients, methicillin-sensitive *Staphylococcus aureus* (MSSA) in 13 patients and methicillin-resistant *Staphylococcus aureus* (MRSA) in 7 patients.

## *Surgical treatment*

The numbers of patients in the different treatment groups are shown in the Figure. Staged revision was successful in most patients (85%). Debridement, antibiotics (antifungals), irrigation, and retention of the prosthesis (DAIR) was successful in 4 of 22 patients, one-stage revision in 1 of 2 patients, and antifungal treatment without surgery in 0 of 3 patients. The mean interval between resection and reimplantation was 4.8 months, ranging from 1 week to 1.5 years. In 55 patients with staged revision, interval duration and treatment outcome were both described, of which only 3 patients in whom treatment failed (mean interval for success 4.2 months vs. 2.8 months for failure). Interval duration of 6 weeks or less was described for 5 patients (all healed), 2 months or less for 19 patients (all healed), and 3 months or less for 34 patients (32 healed).

The use of a spacer was described in 86 patients. 68 spacers were loaded with antibiotic agents, 5 with antifungal agents, and 7 with both. The exact doses of antifungal agents were mentioned by 7 authors. Antifungal drugs used were amphotericin B in 9 patients (between 187.5 mg and 1,200 mg per batch of bone cement (40 g), amphotericin B and variconazole in 1 patient (250 mg and 1,000 mg per batch, respectively), fluconazole in 1 patient (200 mg in a spacer), and itraconazole in 1 patient (250 mg in a spacer). In 2 patients, fluconazole-loaded bone cement beads were implanted (2,000 mg per batch of bone cement).

## *Antifungal therapy*

160 of 164 patients were treated with systemic antifungal agents, mostly with amphotericin B (71 patients) or fluconazole (80 patients). A combination of both was used in 4 patients. All fluconazole use was described in studies after 1996 (70/80 patients between 2002 and 2012). Ampho-

tericin B was more frequently used in earlier studies (44/71 patients between 2002 and 2012). The use of echinocandins, a new group of antifungal agents, was described in 6 patients (2005–2012): caspofungin in 3, micafungin in 2, and anidafungin in 1.

In 143 patients, the total duration of antifungal treatment was mentioned (intravenous and oral combined), with a mean of 3.8 (0–36) months. 7 other patients received chronic antifungal therapy at follow-up.

54 patients who underwent a staged revision had a follow-up of more than 2 years and an adequate description of antifungal treatment duration; 48 of them were treated successfully. Failures (n = 6) had antifungal therapy for a mean of 5.7 (2.5–12) months. Successfully treated patients were given antifungal agents for a shorter period (mean 2.9 months).

Antifungal agent administration of 0–6 weeks was described in 13 patients (n = 13), with success in all. 0–2 months was reported in 28 patients, who all healed. 0–3 months was described in 40 patients (38 of whom healed), and 0–6 months in 48 patients (44 of whom healed).

## Discussion

### *Risk factors*

Risk factors usually associated with fungal infections, more specifically with candidiasis, are mostly factors related to comorbidity with an impaired immune response: an immunosuppressive or immunodeficient status, diabetes mellitus, rheumatoid arthritis, malignancy, tuberculosis, and/or a history of renal transplantation or insufficiency (Azzam et al. 2009, Kelesidis and Tsiodras 2010, Anagnostakos et al. 2012). Other, external factors include drug abuse, prolonged antibiotic use, in-dwelling catheters, malnutrition, severe burns, and multiple abdominal surgeries (Azzam et al. 2009, Kelesidis and Tsiodras 2010, Anagnostakos et al. 2012). These factors are also assumed to play a role in fungal prosthetic joint infection. Other predominant factors include previous PJI, revision surgery, and cutaneous candidiasis (Azzam et al. 2009, Dutronc et al. 2010, Kelesidis and Tsiodras 2010, Garcia-Oltra et al. 2011, Wu and Hsu 2011, Anagnostakos et al. 2012, Chiu et al. 2013). Azzam et al. (2009) showed that around 50% of patients with fungal PJI had 1 or more risk factors, including cardiac disease. However, we found that 101 of 148 patients had one or more risk factors for fungal PJI (68% of the patients), not including cardiac disease as a risk factor. When we included cardiac disease, 82% of the patients were at risk (122/148).

### *Clinical features and diagnosis*

The route of infection for fungal PJI remains controversial. The mechanism and clinical features often mimic that of chronic bacterial infection, with an indolent onset, and most often patients present with swelling and pain without other symptoms of infection (Darouiche et al. 1989, Lerch et al. 2003, Azzam et al. 2009, Dutronc et al. 2010, Chiu et al. 2013). Prosthetic loosening is seen in many patients, as the infection may have been lingering for years (Lambertus et al. 1988, Brooks and Pupparo 1998). We found that half of the patients had radiographic signs of loosening. This is comparable to patients with bacterial PJIs (Bernard et al. 2004). As fungal PJI develops slowly, diagnosis is difficult, and the diagnosis 'aseptic loosening' is easily made—especially with no bacterial co-infection (Lerch et al. 2003).

Most authors agree that serum values, such as CRP and ESR, and joint fluid cell counts have limited value. Discrimination between fungal and bacterial PJI is impossible based on laboratory values. The value of additional tests such as bone scintigraphy and serum titers remains unclear (Paul et al. 1992, Kelesidis and Tsiodras 2010, Anagnostakos et al. 2012).

The diagnosis should be based on cultures from aspiration fluid or tissue or swabs obtained at surgery. However, a substantial delay in diagnosis may occur because culture results are sometimes interpreted as contamination, and most authors recommend obtaining multiple samples, prolonged culture, and special staining (Ramamohan et al. 2001, Yang et al. 2001, Azzam et al. 2009, Dutronc et al. 2010, Chiu et al. 2013). Furthermore, according to Dutronc et al. (2010), if candida species are cultured, they should always be treated as a pathogen. We found that in 21% of the patients, the fungal culture result was—incorrectly—considered to be contamination. We recommend that a cultured fungal species should always be considered to be a pathogen.

Because diagnosis with the above-mentioned microbiological methods may be difficult, other methods such as polymerase chain reaction (PCR) may be useful. However, none of the articles on fungal PJI mentioned PCR.

### *Treatment*

Primary antifungal drug treatment, without surgical treatment, was described in only 3 patients with adequate follow-up, none of which healed. DAIR was successful in 4 of 22 patients. For bacterial PJI, the consensus is that chronic infections should never be treated with DAIR (Crockarell et al. 1998, Osmon et al. 2013). We suggest the same for fungal PJI.

1-stage revision, performed in 2 patients, was successful in 1 patient and unsuccessful in the other (Simonian et al. 1997, Selmon et al. 1998). These numbers are too small to draw any conclusions about 1-stage revision as an alternative to 2-stage revision for fungal PJI.

Many authors have treated fungal PJI as a chronic bacterial infection, and staged revision is generally recommended (Darouiche et al. 1989, Lerch et al. 2003, Azzam et al. 2009, Dutronc et al. 2010, Chiu et al. 2013). In our series, this treatment was commonest, with a success rate of 85% (67/79 patients). The success rate of staged revisions for bacterial PJIs is approximately 87–91% (Garvin and Hanssen 1995, Sia et al. 2005,van Diemen et al. 2013).

The ideal interval between implant removal and reimplantation is unknown. We found a mean of 4.8 months, with a range from 1 week to 1.5 years. Some authors have suggested a 3-month period (Evans and Nelson 1990, Yang et al. 2001) whereas others have advised reimplantation only when repeated (aspiration) cultures are negative (Phelan et al. 2002, Chiu et al. 2013). The time between resection and reimplantation arthroplasty was mentioned for only 3 patients with failure of staged revision (mean 2.8 months as opposed to 4.2 months in the successfully treated patients). The group of patients in which the interval was adequately mentioned may not have been representative for the whole group of fungal PJI patients. Apart from a minimum of 6 weeks, we do not dare to make recommendations on the duration of the resection reimplantation interval. We therefore recommend that reimplantation should be performed only in the absence of clinical signs of infectious symptoms, with CRP and ESR serum levels within the normal range (CRP < 5.0 mg/L and ESR < 10 mm/h) or showing continuously falling values.

The use of local antifungal treatment was described in 14 patients (2 beads, 12 spacers) (Selmon et al. 1998, Bruce et al. 2001, Marra et al. 2001, Phelan et al. 2002, Gaston and Ogden 2004, Gottesman-Yekutieli et al. 2011, Wu and Hsu 2011, Deelstra et al. 2013). 2 groups reported high local levels of antifungal agent with this method (Bruce et al. 2001, Marra et al. 2001), but others claimed that local antifungal therapy had no effect, based on laboratory studies (Wyman et al. 2002, Azzam et al. 2009). An antibiotic-loaded spacer to treat bacterial co-infection or prevent bacterial superinfection was used in 75 patients (Azzam et al. 2009, Anagnostakos et al. 2012, Deelstra et al. 2013). No specific recommendations about the use of antifungal treatment in cement can be made because of the low number of patients. However, adding antibiotics to the cement is advisable because of the high number of patients with a combined fungal and bacterial PJI (33%).

### *Antifungal therapy*

Most authors suggested a minimum duration of treatment of 6 weeks (Ramamohan et al. 2001, Phelan et al. 2002, Anagnostakos et al. 2012), but others advised a minimum of 12 months (Azzam et al. 2009, Austen et al. 2013). Amphotericin B or fluconazole have been considered the drugs of choice for administration in fungal infections (Gaston and Ogden 2004, Antony et al. 2008, Austen et al. 2013). All fluconazole treatments were described in studies reported after 1996. This can be explained by the time of development of the products, and by the publication of studies that indicate that fluconazole is as effective for hematogenous candidiasis yet better tolerated than amphotericin B (Rex et al. 1994). Amphotericin B is one of the most toxic antimicrobial drugs, with a high incidence of adverse effects (Merrer et al. 2001). On the other hand, primary resistance against fluconazole is common in some non-*albicans* candida species, particularly *Candida krusei* and *Candida glabrata* (Selmon et al. 1998, Kontoyiannis and Lewis 2002).

The use of echocandins was only described in a few reports (Lejko-Zupanc et al. 2005, Dumaine et al. 2008, Bland and Thomas 2009, Graw et al. 2010), but it may be a good alternative—due to its low toxicity and broad spectrum—especially for fluconazole-resistant fungal species, or if amphotericin B is not tolerated by the patient. However, the long-term side effects are unclear (Kelesidis and Tsiodras 2010).

The period of antifungal treatment was shorter in successfully treated patients than in patients with treatment failure. This might be due to several factors, including selection bias (e.g. patients in a worse condition may be treated longer) and publication bias (e.g. patients cured with a short antifungal period may be more interesting to publish). Longer treatment may be bothersome for some patients. We concur with other authors, and because duration (comparing 6 weeks and 3 months of antifungal treatment) does not appear to influence outcome after reimplantation, we recommend antifungal treatment for at least 6 weeks, which may be extended until serum CRP and ESR levels have normalized or show continuously falling values, and clinical signs of infection remain absent. There is no evidence that a shorter period of antifungal treatment will give the same results.

## *Conclusion*

68% of the patients with fungal PJI had 1 or more risk factors predisposing for fungal PJI. The majority of these patients presented with signs and symptoms similar to those of chronic bacterial PJIs, such as pain, swelling, and prosthetic loosening. The diagnostic tools are the same for both kinds of infection, as recommended by the Workgroup of the Musculoskeletal Infection Society (Parvizi et al. 2011). Cultured fungi, including candida species, should be considered pathogenic. In the future, DNA techniques such as PCR could assist in the diagnosis, and might even prove to be more accurate than culture (Osmon et al. 2013).

Based on our findings, we recommend 2-stage revision for all patients with a fungal PJI. There is no evidence that 1-stage revision, DAIR, or only antifungal therapy have similar results. Based on our findings, we recommend giving systemic antifungal treatment at least until there are no clinical signs of infectious symptoms, with normalized infection parameters in blood. After that, reimplantation can be considered or performed. There is insufficient evidence that the use of local antifungal treatment has additional benefits. Systemic and local antibacterial drugs should be added (to the cement) when there is co-infection with bacteria.

## *Supplementary data*

Tables 1 and 2 are available at Acta's website (www.actaorthop.org), identification number 6483.

JK, MB, and SC conceived and designed the study. JK and SC performed the literature search. JK, SC, and JS analyzed the data and wrote the manuscript. All authors contributed to interpretation of the data and revision of the final manuscript.

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