Fungal peri-prosthetic infections of the knee and hip are rare but likely to result in devastating complications. In this study we evaluated the results of their management using a single-stage exchange technique. Between 2001 and 2011, 14 patients (ten hips, four knees) were treated for a peri-prosthetic fungal infection. One patient was excluded because revision surgery was not possible owing to a large acetabular defect. One patient developed a further infection two months post-operatively and was excluded from the analysis. Two patients died of unrelated causes.

After a mean of seven years (3 to 11) a total of ten patients were available for follow-up. One patient, undergoing revision replacement of the hip, had a post-operative dislocation. Another patient, undergoing revision replacement of the knee, developed a wound infection and required revision 29 months post-operatively following a peri-prosthetic femoral fracture. The mean Harris hip score increased to 74 points (63 to 84; p < 0.02) in those undergoing revision replacement of the hip, and the mean Hospital for Special Surgery knee score increased to 75 points (70 to 80; p < 0.01) in those undergoing revision replacement of the knee.

A single-stage revision following fungal peri-prosthetic infection is feasible, with an acceptable rate of a satisfactory outcome.

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Fungal prosthetic joint infection (PJI) presents particular challenges for the surgeon, including making the diagnosis and the detection of organisms, the differing pathophysiology of disease, and the nature of systemic and topical antifungal therapy which is required. There remains controversy regarding the elution properties of antifungal agents in bone cement, and the dose required in the treatment of deep fungal infections. A major complication of the systemic use of antifungal agents is the risk of side effects.

Most authors recommend a two-stage procedure for the management of fungal PJI, with or without the use of a cement spacer. The rates of recurrent infection vary widely, between 0% and 25%. The aim of this retrospective study was to evaluate a single-stage exchange approach in the treatment of patients with fungal PJI.

Patients and Methods
Between April 2001 and December 2011, 14 patients (nine men) with a fungal PJI were treated. At the latest follow-up, two patients had died from unrelated causes. Another had an early recurrence of fungal infection two weeks post-operatively and was excluded in order to achieve a more homogeneous group. A fourth was excluded because a resection arthroplasty had been used owing to extensive destruction of the acetabulum with a large associated pelvic abscess. The study, which therefore included ten patients (six hips and four knees) had ethical approval.

The patients completed a Harris hip score (HHS) or a Hospital for Special Surgery (HSS) knee score. Serial plain radiographs were assessed. The mean follow-up was seven years (3 to 11). The characteristics and comorbidities of the patients are shown in Tables I and II. The mean age of the patients was 68 years (31 to 88) at the time of the single-stage exchange. The mean time between the most recent surgical procedure and the onset of further symptoms was 25 months (1 to 168). The diagnosis of infection was made in all patients in accordance with the Musculoskeletal Infection Society algorithm. Failure of the single-stage exchange due to recurrent infection was assumed when the same criteria were applied at the time of any subsequent revision surgery.

A requirement for a single-stage exchange is a knowledge of the organism and its antibiotic sensitivity profile. Therefore, a joint aspiration was performed in all patients.
were stopped at least two weeks before aspiration. The sample of synovial fluid was incubated for 14 days. All samples were placed in sterile tubes without any additional substrates and stored in an airtight anaerobic container with a chemically created moist oxygen-free atmosphere. The specimens were Gram-stained and injected into Brain Heart Infusion broth (BHI; bioMérieux, Marcy l’Étoile, France), thioglycollate-meat-liver serum medium and special media according to Lodenkämper and Stinen. They were then smeared onto Columbia blood (aerobic, 5% CO2; bioMérieux) and Brucella agar (anaerobic; bio-Mérieux) plates and incubated. Sensitivity testing was carried out according to the Deutsches Institut fuer Normung (DIN) Standard 58940.

In all patients with an infected total hip replacement (THR) a posterior approach was used at the time of single-stage exchange. In patients with an infected total knee replacements (TKR) the mid-vastus approach was used. A minimum of five biopsies were taken from around the implants, and processed as described above. Intra-operative wound irrigation was performed using pulsatile lavage with polyhexanide (Lavasept, Fresenius-Kabi AG, Bad Homburg, Germany) prior to implantation of the new prosthesis.

All six revision THRs involved a cemented all-polyethylene acetabular component and a cemented femoral component (Mark III acetabular component and SPII femoral component, Waldemar Link Co, Hamburg, Germany), and all four revision TKRs involved a cemented rotating hinge (Waldemar Link Co). Appropriate antibiotics were added to the cement, based on the cultures and the recommendations of a microbiologist, up to a maximum of 10% antibiotic admixture per package of cement. Cement impregnated with three antibiotics (gentamicin, clindamycin and vancomycin) was used for those patients with a history of previous bacterial infection. In patients with no history of bacterial infection, cement with gentamicin and clindamycin was used. Antifungal agents such as amphotericin B were not added, owing to their poor elution.

The specific post-operative antifungal treatment was based on the pre-operative aspiration and individual sensitivities of the fungus. In order to reach a therapeutic level of intravenous antifungal antibiotics, treatment was started three days pre-operatively. All patients were allowed full weight-bearing post-operatively and had a conventional course of physiotherapy and rehabilitation. Post-operative

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**Table I.** Demographic characteristics of the patients

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age</th>
<th>Gender</th>
<th>Joint</th>
<th>Duration of infection (months)</th>
<th>Fungal reinfection</th>
<th>Reoperation*</th>
<th>Time to reoperation (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>M</td>
<td>Hip</td>
<td>6</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>F</td>
<td>Hip</td>
<td>1</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>M</td>
<td>Hip</td>
<td>168</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>M</td>
<td>Hip</td>
<td>4</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>F</td>
<td>Hip</td>
<td>8</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>M</td>
<td>Hip</td>
<td>18</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>Knee</td>
<td>21</td>
<td>Yes M OE</td>
<td>8 and 24</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>F</td>
<td>Knee</td>
<td>3</td>
<td>No</td>
<td>SI, PF</td>
<td>1 and 116</td>
</tr>
<tr>
<td>9</td>
<td>74</td>
<td>M</td>
<td>Knee</td>
<td>5</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>M</td>
<td>Knee</td>
<td>17</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

* OE: repetition of the single-stage exchange; SI: surgical irrigation of the wound in cause of wound healing disturbance; PF: revision because of peri-prosthetic fracture

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**Table II.** Characteristics of the patient cohort. All patients with a bacterial PJI were treated with a minimum of one two-stage exchange at other institutions

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Joint</th>
<th>Comorbidities</th>
<th>Charlson-Index</th>
<th>Fistula</th>
<th>Number of operations</th>
<th>History of bacterial PJI prior to fungal PJI</th>
<th>Already treated fungal PJI</th>
<th>Time onset symptoms to last surgery (months)</th>
<th>Time onset symptoms to revision (months)</th>
<th>Re-infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>M</td>
<td>Hip</td>
<td>DM</td>
<td>1 Yes</td>
<td>Yes</td>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>F</td>
<td>Hip</td>
<td>DM, DE</td>
<td>2 No</td>
<td>No</td>
<td>4</td>
<td>None</td>
<td>No</td>
<td>1</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>F</td>
<td>Hip</td>
<td>none</td>
<td>0 No</td>
<td>3</td>
<td>None</td>
<td>None</td>
<td>No</td>
<td>8</td>
<td>168</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>M</td>
<td>Hip</td>
<td>DM, COPD</td>
<td>2 Yes</td>
<td>Yes</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>1</td>
<td>4</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>F</td>
<td>Hip</td>
<td>none</td>
<td>1 Yes</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>26</td>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>M</td>
<td>Hip</td>
<td>DA, LC</td>
<td>3 No</td>
<td>4</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>4</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>Knee</td>
<td>DM, CA, PVD, COPD</td>
<td>6 No</td>
<td>1</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>1</td>
<td>21</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>F</td>
<td>Knee</td>
<td>none</td>
<td>0 Yes</td>
<td>8</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>2</td>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>74</td>
<td>M</td>
<td>Knee</td>
<td>MI, COPD</td>
<td>2 Yes</td>
<td>13</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>12</td>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>46</td>
<td>M</td>
<td>Knee</td>
<td>none</td>
<td>0 No</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
<td>17</td>
<td>No</td>
</tr>
</tbody>
</table>

* M, male; F, female; DM, diabetes mellitus; RF, renal failure; DE, dementia; COPD, chronic obstructive lung disease; CA, cancer; DA, intravenous drug abuse; LC, liver cirrhosis; PVD, peripheral vascular disease; MI, myocardial infarction
intravenous antifungal treatment was continued based on the patients’ clinical signs and monitoring of C-reactive protein (CRP) and white blood cell count (WBC).

**Statistical analysis.** Statistical analysis was performed using unpaired Student’s *t*-test. A *p*-value of < 0.05 was considered statistically significant. Statistical analysis was carried out by means of a statistical software package (GraphPad Prism Version 6.04, GraphPad Software Inc., La Jolla, California).

**Results**

The mean pre-operative HHS and HSS scores were 36.8 points (3 to 64) and 51 points (39 to 62) respectively. At the final follow-up, the mean HHS had increased significantly to 74 points (63 to 84; *p* < 0.02). The mean HSS also increased significantly to 75 points (70 to 80; *p* < 0.01).

One patient with a THR had a 1 mm to 2 mm radiolucency around the acetabular component. The patient had no pain and the lucency was non-progressive. No revision has subsequently been performed.

Table III shows the spectrum of bacterial growth in patients with bacterial PJI prior to the fungal infection. Intra-operative samples confirmed the fungal growth in all but one patient, even though antifungal treatment was started three days pre-operatively. Intravenous antifungal treatment continued for a mean of ten days (6 to 21) and orally thereafter for a mean of five weeks (3 to 12) post-operatively.

At the time of admission to hospital, the pre-operative CRP was raised in every patient, with a mean of 22 mg/l (6 to 90.1 mg/l; normal < 5.0 mg/l). In contrast, the WBC was not raised in any patient (mean 5.7 cells/ml) (4.6 to 8.0). At discharge from hospital the mean CRP was 19.0 mg/l (4 to 34.3). At the final follow-up all had normal levels of CRP (< 5.0 mg/l) and a normal WBC level with a mean of 6.2 cells/ml (4.8 to 10).

There was one dislocation of a THR. The two patients who died also had a dislocation not related to their deaths; nor were their deaths related to the surgery. One patient with a TKR had delayed wound healing and subsequently underwent exploration without revision of the components. There was no sign of infection. This patient suffered a peri-prosthetic femoral fracture 29 months post-operatively. At this revision no bacterial or fungal growth was detected. In one patient with a TKR, further infection with *Candida parapsilosis* required revision with a second single-stage exchange, two months post-operatively. This patient, who is immunocompromised as a result of steroid use for > 15 years for chronic obstructive lung disease also has diabetes mellitus and developed recurrent necrosis of the skin, requiring soft-tissue reconstruction on two occasions. One year later, he presented with a sinus and aspiration and intra-operative samples showed growth of *Staphylococcus epidermidis*. A third single-stage exchange revision was undertaken and there have been no further signs of infection for > 1.7 years.

Thus, at a mean follow-up of seven years, there has been one further infection.

**Discussion**

Based on the expected increase in the number of bacterial PJIs, it has been assumed that the number of fungal PJIs will also increase. The rarity of fungal infections limits our understanding of the management and outcome in these patients. However, they often present with immunodeficiency states, or following several revisions of the infected joint, or a history of PJI due to bacteria.

Until recently, there has been no agreement as to how fungal PJIs should be treated. As of August 2013, the International Consensus Group has found some general agreement, but no definitive guidelines or recommendations for the treatment of fungal PJI.

It has been shown that debridement alone, without removal of the infected components, or antibiotic treatment alone, results in a high rate of recurrent infection. In most institutions the preferred technique for treating fungal PJI is a
two-stage revision, with or without the use of a cement spacer; resection arthroplasty is the next favoured option. In a multi-institutional retrospective study Azzam et al reported recurrent infection in ten of 19 patients who had been treated with resection arthroplasty and delayed reimplantation of the prosthesis. In contrast, the largest multi-institutional retrospective study, by Hwang et al, with 30 fungal infections in TKRs, reported a rate of reinfection of 6.6%. In a single-institution retrospective study of two-stage revision in seven patients with fungal infection (four THRs and three TKRs), Anagnostakos et al reported no recurrent infections after a mean of 28 months (5 to 70). Single-stage exchange has been described only once, by Selmon et al in 1998, in a case report of a fungal TKR infection.

The main limitation of this study, apart from its retrospective design, was the small number of patients. However, owing to the uncommon nature of this problem, this still represents a large cohort from a single institution using standardised infection protocols, operative techniques and diagnostic algorithms. The detection of a specific organism and its individual antibiotic sensitivities is essential for a successful single-stage revision. Therefore, antibiotics should be stopped at least two weeks before aspiration, which must be undertaken under strict aseptic conditions and without using local anaesthetic. The incubation of the specimens should continue for 14 days. In contrast to patients with a conventional bacterial PJII, we abstain from adding specific antifungal agents to the bone cement because of the poor elution of antifungal agents from cement.

Because seven patients (70%) in our study had a prior history of bacterial PJII, coexistent recurrent bacterial infection at the time of revision could not be excluded, even in those with negative synovial cultures pre-operatively. Therefore, we used cement that was impregnated with gentamicin, clindamycin and, in most patients, vancomycin, or an appropriately specific antibiotic. This admixture was up to a maximum of 10% antibiotic per package of cement in those with bacterial PJII. The general phenomenon of coexistent bacterial and fungal PJII has been described previously and this led us to believe that patients with fungal PJII should be assumed to have a bacterial infection as well.

As with most previous studies, the most commonly identified fungus was Candida albicans, which comprised the infecting organism identified per-operatively in five patients (50%). Interestingly, C. albicans was only detected in patients undergoing revision THR, whereas C. parapsilosis was only detected in those undergoing revision TKR. Previously, Azzam et al, in a meta-analysis of the English-language literature between 1979 and 2008, found that C. parapsilosis was the most common fungus in PJII complicating TKR, representing 39% of infections. Hwang et al detected C. parapsilosis in 50% of their 30 fungal TKR PJIs. However, this distinction was limited by the small number of patients included in these studies.

Hwang et al proposed the administration of antibiotics for a minimum of six weeks or until the second stage was undertaken. The mean time to reimplantation in their series was 9.5 weeks (6 to 24), and they suggested that treatment with oral antibiotics should subsequently be continued for six months. Azzam et al recommended that intravenous antibiotic treatment should continue for a minimum of six weeks between stages, with a further six months of oral fluconazole after the second stage. The mean time between stages was 28 weeks (8 to 56). Anagnostakos et al administered antibiotics for a minimum of six weeks prior to the second stage, and the mean time between stages was 12 weeks (12 to 14).

There is no direct evidence to support specific periods of antimicrobial treatment, and the side effects of antifungal agents are well known. In contrast to other studies, our patients received intravenous treatment for a mean of ten days. Depending on the clinical features, CRP values and wound healing, oral antibiotics were then continued for a mean of five weeks post-operatively and no side effects, such as acute renal or hepatic failure, were observed.

In conclusion, a single-stage exchange is an effective method of treating fungal PJII. In this study, only one reinfection was seen in a group of ten patients at a mean follow-up of seven years. Conditions for a successful single-stage exchange are incorporated into a complex pre-, intra- and post-operative treatment plan. This plan must be made in accordance with strict institutional protocols, and with the collaboration of an experienced microbiologist.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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References