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Candida albicans prosthetic hip infection in elderly patients: Is fluconazole monotherapy an option?

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Abstract

The increasing numbers of joint arthroplasties being undertaken, and the increase in patients with systemic illnesses undergoing the procedure, have contributed to a continuing increase in prosthetic joint infections. Candida prosthetic joint infection is a rare clinical entity, and only 12 cases of Candida albicans prosthetic hip infection have been described. Although surgery combined with a long period of antifungal medication is the usual treatment for fungal prosthetic joint infections, monotherapy with antifungal agents has only very rarely been used as a therapeutic option, especially in debilitated and elderly patients. We report herein the second case, to our knowledge, of C. albicans prosthetic hip arthritis successfully treated with fluconazole monotherapy and review the literature on the pathogenesis, clinical manifestations and management of these infections. Further studies on the use of fluconazole in the management of fungal prosthetic infections are needed.

Introduction

Candida prosthetic joint infection is a rare clinical entity [1]. Only 12 cases of Candida albicans prosthetic hip infections have been described (Table I). Surgery followed by a long period of antifungals is the usual treatment. Conservative therapy with antifungal agents alone has rarely been used as a therapeutic intervention for the management of these infections, particularly in debilitated and elderly patients. Only 4 cases of successful treatment of C. albicans prosthetic joint infection without prosthesis removal where fluconazole was used have been reported [2–5]. Fluconazole monotherapy provides an attractive primary option for the treatment of Candida prosthetic joint infections, particularly for debilitated and elderly patients. We report the second case, to our knowledge, of C. albicans prosthetic hip arthritis successfully treated with fluconazole alone and review the literature on the pathogenesis, clinical manifestations and management of these infections.

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Review of the literature

All previous cases included in our literature review were found using a PubMed search (1975–May 2009) of the English language medical literature, applying the terms ‘Candida’, ‘prosthetic joint infection’, ‘hip’, ‘infection’. We examined the references cited in these articles to identify additional reports.

Case report

A 93-y-old female patient with multiple medical problems presented with increasing right hip pain of 2-week duration. She reported an open reduction and internal fixation and right hip hemiarthroplasty of a right displaced femoral neck fracture 5 months prior to admission. Her postoperative course was complicated by multiple dislocations of the right hip and surgical attempts for reduction. Routine cultures of the hip taken during revision arthroplasties were negative for any pathogen. Due to worsening right hip pain for a period of 2 weeks, she was admitted. On admission, the patient was afebrile, and physical examination revealed tenderness to palpation of the right hip and decreased and painful range of motion in all directions. No overlying redness or swelling was noted. Laboratory parameters disclosed a white blood cell count of 6700/mm^3 (70% neutrophils, 25% lymphocytes, 4% monocytes), an elevated erythrocyte sedimentation rate (90 mm/h), highly sensitive C-reactive protein (CRP) of 8.3 mg/l and a low albumin of 2.9 g/dl. Radiography of the hip disclosed signs of implant loosening. After extensive discussions with the patient and her family, the decision was made to proceed with constrained right total hip replacement. Swabs and tissue samples collected intraoperatively were cultured, and Gram stain was negative for any pathogens. Cultures of joint fluid and tissue sample grew C. albicans sensitive to fluconazole (minimum inhibitory concentration (MIC) 1.25 μg/ml). Based on the patient’s history of extensive manipulations of the right hip, her comorbidities and the wishes of the patient and her family, a conservative approach with fluconazole monotherapy (400 mg/day i.v.) for 6 weeks without any further surgical intervention was elected. Gradual resolution of all her discomfort was observed. She continued with maintenance fluconazole (400 mg/day orally) indefinitely. One y into her follow-up she remains asymptomatic and well. An X-ray of the right hip showed a well-aligned total hip prosthesis and laboratory evaluation disclosed an erythrocyte sedimentation rate of 60 mm/h and highly sensitive CRP of 2.2 mg/l.

Results

Infection after total hip arthroplasty is a rare but potentially devastating complication. The infection rate is estimated to range between 0.5% and 5% of all joint arthroplasties [1]. The actual incidence of fungal infections involving prosthetic joints is unknown, but it is estimated to constitute about 1% of all prosthetic joint infections [6]; most of these infections are caused by Candida spp. [7]. According to a previous review, C. albicans is the most frequently involved species, followed by Candida parapsilosis, Candida tropicalis and Candida glabrata [1]. Only 46 cases of Candida prosthetic arthritis have been reported in the literature (up until May 2009) [1–6, 8–35]. The prosthetic joints involved were: the knee (24 cases, 52.2%) [1,3–6,8,9,12–16,18–20,22,25–28,30,31,34,35], hip (19 cases, 41.3%) [1,2,6,9,11,14,17,21,23,29,32,33], shoulder (2 cases, 4.4%) [10,12] and

metacarpophalangeal joint (1 case) [24]. From 19 cases of Candida prosthetic hip joint infections that we identified [1,2,6,9,11,14,17,21,23,29,32,33], isolated organisms were: C. albicans (12 cases, 63.2%) [1,2,6,17,21,32], C. glabrata (4 cases, 21%) [9,23,29,33], C. tropicalis (2 cases, 10.5%) [6,14], and C. parapsilosis (1 case, 5.3%) [11]. We further analyzed the 12 cases of C. albicans prosthetic hip infection. The age of the patients ranged from 44 to 83 y with a median age of 67 y, with equal numbers of males and females. Underlying conditions included prior prosthetic joint infection (6/12, 44.5%) [1,21,32], prior Candida infection (4/12, 33.4%) [1,32], prior history of multiple surgeries of the prosthetic joint (4/12, 33.4%) [1,17,21], rheumatoid arthritis (3/12, 25%) [1,17,21], diabetes mellitus (2/12, 16.7%) [2,6], antibiotic use (1/12, 8.3%) [1], prior abdominal surgery (1/12, 8.3%) [2], renal transplantation and immunosuppressive treatment [21], alcoholism (1/12, 8.3%) [21], and leukaemia (1/12, 8.3%) [32]. No underlying conditions were reported in 2 cases (2/12, 16.7%) [6,17]. The presenting symptoms included mild to moderate swelling and pain, with decreased range of motion almost a universal finding. However, no patient presented with significant erythema or constitutional symptoms suggestive of infection. Only 3 patients exhibited leukocytosis on presentation [6,21,32]. Drainage from the incision site was noted in 3 patients (2 with bacterial co-infection of the prosthetic joint [15,21]). In all cases there was radiographic evidence of loosening of involved joints. The joint fluid was exudative or purulent, with granulocyte cell predominance in every case for which data were available. Only 1 patient had a documented Gram stain positive for Candida [6], whereas cultures were always positive for Candida. No patient had positive blood cultures, and only 1 patient had a positive urine culture [21]. In only 2 cases was the MIC of the C. albicans isolate for fluconazole documented (1.25 μg/ml) [1]. The majority (11/12 (91.7%) patients) required resection arthroplasty or debridement for eradication of the fungal infection [1,6,17,21,32]. Medical therapy consisted of amphotericin B [1,6,17,21,32] in 9 cases, followed by oral ketoconazole in 1 case [1] or fluconazole in 3 cases [1,1,21]. Fluconazole was used as monotherapy in only 1 case [2]. Neither the dosage nor the duration of antifungal treatment was consistent in any of the patients (see Table I). Replacement of the prosthesis was done in 5 of these individuals [1,17]. It was claimed that 1 patient was cured after medical therapy alone with fluconazole despite the continued presence of the prosthesis; however, this patient had a resection arthroplasty with antibiotics and subsequent revision arthroplasty [1]. A favourable outcome (as defined by cure or no further recurrence of infection) was reported in 8 cases [1,2,6,17,32]. In 3 cases the patient died of a reason unrelated to the prosthetic joint [2,21]. The duration of follow-up was 5–73 months (average 35 months).

Discussion

Pathogenesis of Candida prosthetic joint infections

Throughout the past 10 y, the number of fungal prosthetic joint infections has been increasing, which may simply reflect the rising number of joint arthroplasties. Risk factors for the development of invasive candidal infections include immunosuppression, neutropenia, chronic or prolonged use of antibiotics, presence of indwelling intravenous catheters, diabetes mellitus, corticosteroids, parenteral hyperalimentation, malnutrition, rheumatoid arthritis, history of multiple abdominal surgeries, history of renal

transplantation, severe burns, and injection drug use [6,8,13,21,22]. Preceding bacterial infection of the prosthesis can also be a risk factor for subsequent fungal infection [6,15,16,21]. Some patients with a prosthetic joint fungal infection have no predisposing condition other than the prosthesis itself [6]. Approximately a half of the reported cases of candidal prosthetic joint infections have no identifiable risk factor [8,26]. The exact mechanism of Candida infection of prosthetic joints is not clear. In contrast to Candida native joint arthritis, which is most often the result of haematogenous dissemination, fungal prosthetic infections most likely result from the inoculation of skin microflora at the time of implantation [11,14] or arthrocentesis [8], particularly in elderly patients [36,37]. In certain cases there is a long interval between surgery and the occurrence of Candida arthritis [2,21]. In such cases, a haematogenous route of infection following unrecognized candidaemia is likely [2]. Direct extension into the synovial space from infected adjacent bone may represent another potential route of candidal infection. Periprosthetic infection might then be promoted by favourable local factors, both mechanical and molecular. The role of prosthetic materials, candidal adhesins, and human factors such as fibronectin in initiating these infections has yet to be determined.

Diagnosis

Diagnosis of joint fungal infections is compromised by difficulty in detecting the fungi, but also by the false interpretation of positive cultures as contaminants. Infection is usually manifested by pain and mild-to-moderate swelling, without apparent inflammation of the affected joint but with a decrease in the range of motion. The clinical and radiological features most often mimic those of mechanical failure. A spirated joint fluid in cases of infection due to Candida species may be serosanguinous or purulent; Gram staining is generally negative for the yeast, due to low cell counts [12]. Thus, the diagnosis is normally established by positive cultures from multiple joint aspirations or from a single aspiration in the proper clinical milieu or from tissue specimen at the time of surgery. However, histological evidence of invasive Candida was not present in any of the reviewed cases of Candida prosthetic joint infection. Physicians should also pay attention to positive cultures from other sites (e.g. urine) as shown by our review. Although serology may assist in certain cases [18], the serodiagnosis of Candida infection is difficult due to the confusion generated by false-positive reactions seen in uninfected individuals whose immune systems have been exposed to the antigens of these ubiquitous commensals and false-negative reactions seen in infected immunodeficient patients [1]. In conclusion, any unusual symptoms and local signs should alert the physician to the possibility of prosthetic joint infection, since prolonged infection facilitates failure of implant surgery.

Treatment

Because of the limited number of reported cases, definite information about the optimal treatment of candidal joint infections is not available. For the antifungal treatment of native joint infections, recent guidelines suggest the use of an initial course of amphotericin B for 2 to 3 weeks, followed by fluconazole for a total of 6 to 12 weeks [38]. However, fungal prosthetic joint infections are extremely difficult to treat. Biofilm formation is believed to be a primary resistance mechanism for Candida spp. [39]. Recent guidelines recommend a similar approach for antifungal therapy for both native joint arthritis and prosthetic joint

infections, with variable duration of therapy depending on the selected antifungal agent [38]. The choice of antifungal agents has varied considerably in the cases reported in the literature.

Amphotericin B has been used most commonly for deep-seated candidal infections. Synovial fluid levels of amphotericin B vary from 20% to 1100% of serum fluid levels, which are sufficient to inhibit growth [40]. In 1 review, the duration of treatment of Candida prosthetic joint infections ranged from 6 weeks to 9 months, with the median being 6 weeks for patients who received amphotericin B, and the mean total dose of amphotericin B, when used alone or in combination with 5-fluorocytosine, was 1552 mg [1]. No studies have been done to document the equivalence of the lipid formulations of amphotericin B to conventional amphotericin B for the treatment of candidal prosthetic joint infections.

Successful treatment of candidal prosthetic joint infections with fluconazole as the only antifungal agent was reported in 4 cases (Table II) [2–4,25]. Both clinical and experimental data demonstrate high in vivo activity of fluconazole against most Candida species, with good synovial fluid penetration [19,25,38], even when fluconazole is used orally [3]. C. albicans is often highly susceptible to this drug [41]. Although data are limited, therapy with fluconazole appears to be as effective as amphotericin B therapy for susceptible strains when combined with adequate surgical drainage. The lower fluconazole toxicity allows lengthier periods of treatment. In one report, the median duration of treatment was slightly more than 17 weeks for patients with Candida prosthetic joint infections who received fluconazole [1].

Newer antifungal agents such as echinocandins may be an attractive alternative for the treatment of fungal prosthetic joint infections given their spectrum of activity, reduced toxicity and ease of administration. They exhibit concentration-dependent fungicidal activity against Candida spp., excellent in vitro penetration into biofilm [34], have a prolonged post-antifungal effect [1] and are very well tolerated, with a low discontinuation rate due to adverse effects. More recently, 2 case reports have shown caspofungin to be an effective treatment for C. glabrata knee and hip infections [42,43]. However, these agents need to be investigated further for treatment of these infections.

The use of antifungal combination therapy is a new clinical approach for combating fungal infections [44] and could be an alternative to monotherapy for patients with invasive infections that are difficult to treat. Very few data exist regarding combination therapy for Candida infections. Some in vitro data suggest either an additive or no effect when combining anidulafungin with various azoles against Candida spp. [45]. Because of the enhanced penetration of biofilm with echinocandins, a combination regimen of an echinocandin plus azole may offer a viable option for these patients, especially when removal of the hardware is not feasible, as was demonstrated in 1 patient who received combination therapy with fluconazole plus micafungin for approximately 8 weeks, followed by fluconazole monotherapy [35]. In another case a prosthetic knee infection was successfully treated with caspofungin and flucytosine [34]. Combination therapy involving amphotericin B plus flucytosine has also been utilized [43]. Until more robust data are available that support combination therapy with retained hardware, removal of the infected

hardware along with antifungal therapy remains the optimal therapy for Candida prosthetic joint infections.

Although antifungal therapy for the treatment of candidal prosthetic joint infections is similar to that used for native joint infections, surgery plays a more important role. For prosthetic hip infections, resection arthroplasty (Girdlestone procedure) has been the most common surgical option used [1] and can be adequate treatment in certain cases [1,14]. However, because of the perceived high risk of recurrence, recent guidelines advise the use of resection arthroplasty with antifungal therapy as the standard treatment [38]. Most patients with candidal prosthetic joint infections undergo permanent prosthesis removal and subsequently have poor functional outcome. Delayed reimplantation arthroplasty offers the best opportunity for a good functional outcome. Decisions on performing a reimplantation should be based on favourable clinical picture and negative cultures after a long follow-up period and not based on leukocyte count, erythrocyte sedimentation rate, and CRP, which may have poor negative predictive value [46] and limited value in immunocompromised patients. The duration of such a follow-up period has not been determined. Current guidelines suggest that reimplantation may be done after successful eradication of the infection, as defined by the lack of recurrent symptoms while the patient is not receiving therapy [38]. However, in a previous report, only 10 (22%) of a total of 46 patients underwent delayed reimplantation arthroplasty for candidal prosthetic joint infections [1]. The duration of treatment may range from 6 weeks to 9 months [1]. Recurrent infection after delayed reimplantation is a serious complication and often results in permanent removal of the joint prosthesis [47–49]. A 20% recurrence rate after 2-stage reimplantation for candidal prosthetic joint infections should be anticipated [1].

Local antifungal therapy is also an option for the treatment of Candida prosthetic joint infections. Amphotericin B-loaded bone cement has been used to treat osteomyelitis caused by C. albicans [1]. Fluconazole-impregnated cement possesses anti-Candida activity and is an effective adjunctive therapy in a rat model of C. albicans foreign-body osteomyelitis [1]. However, it is not known whether revision arthroplasty with medicated bone cement may be an effective method to reduce the rate of secondary deep fungal infections after reimplantation arthroplasty, and further research in this area is necessary.

Although resection arthroplasty remains the gold standard, avoiding unnecessary surgical procedures and anaesthesia is of the utmost importance for elderly or immunosuppressed patients. Removal of the implant was required in order to control the infection in all of the patients reported so far, with the exception of 5 cases where a mycological cure was achieved with fluconazole therapy without removal of the prosthesis [2–5]. Failure with fluconazole treatment has also been reported [20]. There is no consensus on duration of antifungal treatment without replacement of the prosthesis. Although a 1-y course of treatment seems reasonable, a more prolonged or even lifelong treatment course may be necessary. Support of patient compliance and careful monitoring for any clinical signs of relapse is required. Evaluation of whether removal of the implant might be possible should be performed at regular intervals.

Removal of the hardware plus antifungal therapy is considered the primary treatment in the majority of fungal prosthetic joint infections. Our case was unique in that the hardware was not removed and the patient was treated conservatively with antifungal therapy to preserve her mobility. This is the second report of C. albicans prosthetic hip infection treated with fluconazole monotherapy with only 1 other case reported of a patient who had a follow-up of 11 months [5]. Our patient responded to monotherapy with fluconazole and did not require removal of the hardware at 1-y follow-up. She had multiple manipulations of the prosthetic joint with 3 dislocations of her hip, 3 attempts for reductions, 1 prior revision arthroplasty and exposure to antibiotics as predisposing factors for prosthetic joint fungal infection. Based on the patient's wishes and her co-morbidities, oral suppressive therapy with fluconazole was attempted. This approach has been suggested for patients who refuse surgery or debilitated patients with prosthetic joint infections where surgery may carry an unacceptably high risk of morbidity [50]. However, in vitro experiments have demonstrated that fluconazole is unable to eradicate the organism from an established biofilm or prevent biofilm formation [51], which can lead to treatment failure [35]. In our patient, the scraped material from the prosthesis did not show any organism and it was difficult to determine whether a biofilm was involved. We did not interpret the yeast growth as contamination based on pure isolation of the same organism in both aspirated and scraped tissue materials and the rather satisfactory clinical response to antifungal therapy. Factors contributing to successful medical treatment in this case were the patient's intact immune system and the early diagnosis (based on negative cultures 2 months prior to this diagnosis). However, it is important to note that no follow-up period can truly be considered adequate for fungal infections, which have a notoriously indolent pattern of development. Although the infection could resurface in our patient in the future, the clinical response appeared to be satisfactory. We believe that the 1-y follow-up is significant in this 93-y-old patient with multiple co-morbidities, but longer follow-up is necessary in order to reach a definitive conclusion.

Conclusions

The rising numbers of joint arthroplasties and patients with systemic illnesses undergoing hip arthroplasty will contribute to a continuing increase in prosthetic joint infections. C. albicans prosthetic hip infections remain very rare. A combined medical and surgical approach that includes antifungal therapy (either fluconazole and/or amphotericin B) and confirmation of an infection-free period after the initial surgical approach appears to provide the best chance of a successful reimplantation. The optimal duration of antifungal therapy and time to reimplantation remain unknown. However, for elderly debilitated patients, poor surgical candidates or patients who refuse surgery, conservative medical management of these infections with fluconazole can potentially be a good alternative option. High dosages and even lifelong treatment may be needed in cases not initially responding to antifungal treatment [52]. Further studies on the use of fluconazole in the management of fungal prosthetic infections are needed.

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Table I.

Candida albicans prosthetic hip infections.

Author, y [Ref.]	Age (y)	Sex	Underlying conditions	Type of infection	Treatment	Outcome
Lazzarini, 2004 [32]	63	M	Chronic monocytic leukaemia, total hip arthroplasty of the same joint complicated by C. albicans infection 5 months earlier	7 months after the prosthetic joint surgery, the patient developed prosthetic hip infection	Resection arthroplasty, amphotericin B (1 mg/kg, 30 days)	Postoperative course complicated by (1) wound infection (coagulase-negative staphylococci, treated with vancomycin), (2) candidaemia (C. glabrata, treated with central venous catheter removal, amphotericin B (30 days)). No recurrence at follow-up (4 y)
Phelan, 2002 [1]	75	F	Communicating right-groin cyst, rheumatoidarthritis, prior prosthetic joint infection, multiple revisions	Prosthetic hip infection 32.7 months after implantation (for rheumatoid arthritis)	Resection arthroplasty; fl uconazoleimpregnated spacer; fl uconazole for 47 days (200 mg); reimplantation (2.4 months from resection arthroplasty to reimplantation)	Cure (17 months follow-up)
Phelan, 2002 [1]	60	F	Prior candidal prosthetic joint infection	Prosthetic hip infection 14.9 months after implantation (for osteoarthritis)	Resection arthroplasty; amphotericin B for 71 days (1000 mg), then fl uconazole for 269 days (400 mg); reimplantation (12.1 months from resection arthroplasty to reimplantation)	Cure (70 months follow-up)
Phelan, 2002 [1]	83	M	Long-term antibiotic use, chronic Candida cystitis	Prosthetic hip infection 184.2 months after implantation (for Perthes disease)	Resection arthroplasty; amphotericin B for 36 days (500 mg), then ketoconazole for 5 months, then fl uconazole, 25 mg/day for 61 days; reimplantation (17.7 months from resection arthroplasty to reimplantation)	Cure (73 months follow-up)
Merrer, 2001 [2]	81	F	Diabetes, right hemi-colectomy for colonic carcinoma, bilateral total hip arthroplasty 12 y prior (indication NR)	Prosthetic hip arthritis (1 month after right hemicolectomy) treated with fl uconazole alone	Fluconazole was continued for 10 months (400 mg/day for 3 months and then 200 mg/day for 7 months)	No recurrence of infection 6 months after cessation of fl uconazole therapy. Died of an intestinal haemorrhage 11 months after the end of treatment
Cardinal, 1996 [21]	42	F	Renal transplant 20 y earlier, on immunosuppression including corticosteroids. Bilateral total knee and hip replacement (for avascular necrosis). Previous right hip Staphylococcus aureus infection	Infection of right prosthetic hip joint 9 y after revision of right total hip arthroplasty	Resection arthroplasty with Girdlestone procedure. Amphotericin was continued for a total of 2 g	Died of end-stage renal disease before a revision arthroplasty was performed
Cardinal, 1996 [21]	67	F	Rheumatoid arthritis, bilateral total knee and hip replacement (for rheumatoid arthritis). Multiple surgeries	Infection of left prosthetic hip joint 6 weeks after resection arthroplasty of left hip (for Staphylococcus epidermidis)	Debridement, amphotericin B (25 mg/ day) for 6 weeks followed by oral fl uconazole (dose, duration NR)	She had persistent infection with S. epidermidis. She died 1 y later of unrelated cause
Cardinal, 1996 [21]	57	M	Alcoholism, bilateral total hip replacement for post-traumatic avascular necrosis 18 y earlier.	Infection of left prosthetic hip joint 2 y after revision arthroplasty of left hip (for loosening)	Vancomycin, imipenem, fl uconazole (duration NR), debridement after recurrence after 1 month	Recurrent drainage after 1 month (S. epidermidis) treated with methicillin and

Author, y [Ref.]	Age (y)	Sex	Underlying conditions	Type of infection	Treatment	Outcome
			Multiple infections of both prosthetic joints. Multiple surgeries			debridement. Was asymptomatic for 6 months after that
Evans, 1990 [17]	44	M	Rheumatoid arthritis, 2 joint revisions	Prosthetic hip infection 10 months after implantation	Amphotericin B, 50 mg/day for 6 weeks (2100 mg), which was unsuccessful; recurrent prosthetic joint infection after 30 months: no antifungals given; resection arthroplasty; reimplantation (5 months from resection arthroplasty to reimplantation)	Cure (60 months follow-up)
Evans, 1990 [17]	64	M	None reported	Prosthetic hip infection 60 months after implantation (for osteoarthritis)	Resection arthroplasty; amphotericin B, 35 mg/day for 6 weeks (1470 mg); reimplantation (5 months from resection arthroplasty to reimplantation)	Cure (24 months follow-up)
Darouiche, 1989 [6]	62	M	Osteoporosis; diabetes mellitus	Prosthetic hip infection (1 y after implantation, which was done for osteoporosis)	Removal of prosthesis, amphotericin B (30 mg/day, 0.5 mg/kg i.v. for 5 weeks)	No recurrence after 8 months follow-up
Darouiche, 1989 [6]	78	F	None	Prosthetic hip infection (6 months after implantation for osteoarthritis)	Removal of prosthesis, amphotericin B (pre-op 150 mg in total and post-op 25 mg/day for 6 weeks)	No recurrence after 5 months follow-up

NR, not recorded.

Table II.

Candida prosthetic hip infections treated without resection arthroplasty.

Author, y [Ref.]	Age (y)	Sex	Underlying conditions	Type of infection	Treatment	Outcome
Current report	93	F	Chronic obstructive pulmonary disease, coronary artery disease and previous stroke, hypertension, dementia, atrial fi brillation. Pneumonia caused by methicillin-resistant Staphylococcus aureus (MRSA) 2 months prior	C. albicans prosthetic hip arthritis (2 months after 3 recurrent dislocations of the right hip)	Fluconazole (400 mg i.v./day) for 6 weeks with gradual resolution of all her discomfort followed by oral fl uconazole (400 mg/day) indefi nitely	10 months after presentation, follow-up X-ray of the right hip revealed well-aligned total hip prosthesis. Repeat erythrocyte sedimentation rate was 60 mm/h and highly sensitive C-reactive protein, 2.2 mg/l. At follow-up after 1 y the patient remained afebrile, did not have recurrent hip pain and did not have any further falls
Merrer, 2001 [2]	81	F	Diabetes, right hemi-colectomy for colonic carcinoma. Bilateral total hip arthroplasty 12 y prior (indication NR)	C. albicans prosthetic hip arthritis (1 month after right hemicolectomy)	Fluconazole for 10 months (400 mg/day for 3 months and then 200 mg/day for 7 months)	No recurrence of infection 6 months after cessation of fl uconazole therapy. Died of an intestinal haemorrhage 11 months after the end of treatment
Cushing, 1997 [3]	73	F	Total joint arthroplasty	Candida parapsilosis knee infection 30 months after total joint arthroplasty	Fluconazole 400 mg daily for 6 months, followed by maintenance dose of 100 mg orally daily	No recurrence of infection 1 y after intravenous therapy was initiated
Fukasawa, 1997 [4]	80	F	Elderly patient with osteoarthritis	Candida parapsilosis arthritis after total knee 2 months after left knee arthroplasty for osteoarthritis. Co-infection with Pseudomonas aeruginosa	Intra-articular fl uconazole. 1 y of oral fl uconazole treatment (200 mg/day). Ceftazidime, clindamycin for 3 weeks then oral norfl oxacin for 2 weeks	Successful treatment without prosthesis removal (2 y follow-up). The fi rst nonimmunocompromised patient who has been cured without removal of the implant
Simonian, 1997 [5]	76	F	Elderly patient without predisposing medical problems	Candida (species NR) infection of knee 3.5 y after total knee arthroplasty	Treated with only a suppressive dose of ketoconazole (200 mg every day) for 8 months	No recurrence of infection 6 y after the revision surgery
White, 1995 [20]	64	F	Severe osteoarthritis, total right-knee replacement	Candida parapsilosis prosthetic joint infection 8 months after prosthesis	Fluconazole 200 mg/day for 7 months and 400 mg/day for 17 months. Cultures remained positive for Candida parapsilosis. Removal of the prosthetic device 3 y after total knee replacement combined with a 500-mg course of intravenous amphotericin B; bone cultures again yielded C. parapsilosis. Itraconazole (200 mg twice daily) for 5 months	The fi rst documented failure of fl uconazole in the treatment of candidal prosthetic arthritis despite the apparent in vitro susceptibility of the organism to that drug
Tunkel, 1993 [19]	37	M	HIV, haemophilia, prior prosthetic joint infections, multiple joint revisions, prolongedantibiotic therapy	Prosthetic knee infection from Candida parapsilosis 4 months after implantation and revision of previous left total knee replacement	Resection arthroplasty; amphotericin B (880 mg), then ketoconazole given daily (400 mg); reimplantation; recurrence while receiving ketoconazole at 1 month; fl uconazole maintenance, 200 mg/day for 6 months; amputation (4 months from resection arthroplasty to reimplantation)	Treatment failure initially (2 months follow-up). The fi rst case of Candida prosthetic arthritis in which mycologic cure was achieved with fl uconazole despite the continued presence of the prosthesis

NR, not recorded.