Candida periprosthetic joint infection: a rare and difficult-to-treat infection

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PII: S0163-4453(18)30129-4
DOI: [10.1016/j.jinf.2018.03.012](https://doi.org/10.1016/j.jinf.2018.03.012)
Reference: YJINF 4093

To appear in: *Journal of Infection*

Received date: 25 January 2018
Revised date: 1 March 2018
Accepted date: 4 March 2018

Please cite this article as: Laura Escolà-Vergé , Dolors Rodríguez-Pardo , Jaime Lora-Tamayo , Laura Morata , Oscar Murillo , Helem Vilchez , Luisa Sorli , Laura Guío Carrión , José M^a Barbero , Julián Palomino-Nicás , Alberto Bahamonde , Alfredo Jover-Sáenz , Natividad Benito , Rosa Escudero , Marta Fernandez- Sampedro , Rafael Pérez Vidal , Lucía Gómez , Pablo S. Corona , Benito Almirante , Javier Ariza , Carles Pigrau , Study Group on Osteoarticular Infections of the Spanish Society of Clinical Microbiology and Infectious Diseases (GEIO-SEIMC), and the Spanish Network for Research in Infectious Pathology (REIPI), Candida periprosthetic joint infection: a rare and difficult-to-treat infection, *Journal of Infection* (2018), doi: [10.1016/j.jinf.2018.03.012](https://doi.org/10.1016/j.jinf.2018.03.012)

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Highlights

- CPJI is usually a chronic infection occurring in patients of advanced age with comorbidities.
- Success rate is low and treatment with prosthesis removal improves outcome.
- In our experience, antifungals with antibiofilm activity may be recommendable.

ACCEPTED MANUSCRIPT

1. TITLE: *Candida* periprosthetic joint infection: a rare and difficult-to-treat infection

2. A running title of no more than 40 characters and spaces: *Candida* periprosthetic joint infection

3. The names and affiliations of all authors:

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ABSTRACT

Background. *Candida* periprosthetic joint infection (CPJI) is a rare, difficult-to-treat disease. The purpose of this study was to evaluate the clinical characteristics and outcomes of CPJI treated with various surgical and antifungal strategies. **Methods.** We conducted a multicenter retrospective study of all CPJI diagnosed between 2003 and 2015 in 16 Spanish hospitals. **Results.** Forty-three patients included: median age, 75 years, and median Charlson Comorbidity Index score, 4. Thirty-four (79.1%) patients had ≥ 1 risk factor for *Candida* infection. Most common causative species were *C. albicans* and *C. parapsilosis*. Thirty-five patients were evaluable for outcome: overall, treatment succeeded in 17 (48.6%) and failed in 18 (51.4%). Success was 13/20 (67%) in patients with prosthesis removal and 4/15 (27%) with debridement and prosthesis retention ($p=0.041$). All 3 patients who received an

amphotericin B-impregnated cement spacer cured. In the prosthesis removal group, success was 5/6 (83%) with an antibiofilm regimen and 8/13 (62%) with azoles ($p=0.605$). In the debridement and prosthesis retention group, success was 3/10 (30%) with azoles and 1/5 (20%) with antibiofilm agents. Therapeutic failure was due to relapse in 9 patients, need for suppressive treatment in 5, persistent infection in 2, and CPJI-related death in 2; overall attributable mortality was 6%.

Conclusions. CPJI is usually a chronic disease in patients with comorbidities and risk factors for *Candida* infection. Treatment success is low, and prosthesis removal improves outcome. Although there is insufficient evidence that use of antifungals with antibiofilm activity has additional benefits, our experience indicates it may be recommendable.

Keywords: fungal periprosthetic infection, *Candida*, antifungal-loaded bone cement, echinocandins, antibiofilm agents, 2-stage treatment

INTRODUCTION

Surgical procedures involving joint prosthesis implantation are being carried out increasingly more often [1,2]. Infection is one of the most feared complications following these procedures because of the associated comorbidity and possible need for removal of the implant [1–3]. Staphylococci account for more than half of periprosthetic joint infections (PJI). Less than 1% of all PJI are caused by fungi, and *Candida* species are responsible for at least 80% of them [4–6]. *Candida* periprosthetic joint infection (CPJI) poses a challenge, as it is a rare infection and there are no clear guidelines regarding the best management strategies [2,3,7–10].

Candida spp. often grow as a biofilm adhering to a medical device or other surface, such as bioprosthetic implants, including cement spacers [11,12], and this may contribute to persistence and relapse of the infection (8, 9). Various surgical and antifungal medical approaches have been used in the small number of case reports and clinical series focused on CPJI, with high recurrence rates in some articles, particularly when the prosthesis is not removed [4,14–16]. Azoles have been the main agents used in these infections, and reported failure rates are high [4,14,15], likely because the activity of these drugs against biofilms is poor. Amphotericin B and the new echinocandins are both active against biofilms [11,12,17], but their impact in CPJI treatment is uncertain. In addition, it is still unknown whether antifungal-loaded cement spacers may improve cure rates, as was suggested in one study [16].

The aim of this multicenter study was to describe the characteristics of CPJI and analyze the effectiveness of different surgical approaches (prosthesis removal versus retention) and medical treatment strategies (azoles versus antifungals with antibiofilm activity) in patients with this infection.

PATIENTS AND METHODS

Study design, patients, and setting

A retrospective, multicenter study of patients diagnosed with CPJI was conducted in 16 Spanish hospitals that are part of the Study Group on Joint Infections (GEIO, *Grupo de Estudio de Infecciones Osteoarticulares*), and the Spanish Network for Research in Infectious Diseases (REIPI, *Red Española de Investigación en Patología Infecciosa*).

Cases were identified by searching in the dedicated databases of recorded consecutive cases of PJI or in the general archives of each participating hospital. The study included all patients with PJI originally caused by *Candida* spp., diagnosed from January 2003 through December 2015, and meeting the definition of CPJI specified below. *Candida* spp. superinfections of the spacer were excluded.

Data Collection

Clinical data were obtained by medical records review. We collected patient-specific information, including patient characteristics, comorbidities, predisposing risk factors such as previous broad-spectrum antibiotic therapy, the causative organism, type of surgery, type and duration of systemic antifungal therapy, outcome, and time of follow-up. All cases were critically reviewed by L.E. and C.P., and all inconsistent data were checked by the investigator at each collaborating hospital.

Definitions

CPJI was defined based on the following criteria: 1) presence of signs and symptoms of PJI, such as pain, erythema, or other inflammatory signs, plus ≥ 2 cultures positive for *Candida* spp. in deep samples (joint aspirate, surgical specimens) or blood culture; and/or 2) presence of a fistula or pus around the prosthesis found during surgery with ≥ 1 culture positive for *Candida* spp. in deep samples or blood culture, considered to be CPJI and treated as such by the attending physician. PJI type was assigned according to the Tsukayama criteria [18,19]. Early postoperative (<4weeks) and

hematogenous infections were considered acute infections, whereas late chronic and intraoperative culture-positive infections were considered chronic infections.

In accordance with previous reports [4,15], the risk factors for the development of CPJI included comorbidities associated with cellular immunosuppression, previous use of antibiotics, practice of more than one surgery on the joint, and previous infection by *Candida*. In line with previous reports [11,12,17], we considered echinocandins and amphotericin B (systemic or local) to be active against biofilms, and azoles to lack this activity. Patients were clinically followed-up during hospitalization and in the outpatient clinic.

Cure was defined as an absence of signs and symptoms of infection after a minimum follow-up of 2 years. Treatment failure was established based on the following: 1) persistent infection, defined by persistent clinical signs and symptoms of infection during treatment that required a change in the initial strategy; 2) relapse, defined as reappearance of clinical signs and symptoms of infection once the initial clinical-surgical treatment had been completed, with isolation of the same microorganism; 3) need for suppressive treatment, as it was assumed that the patient would not be cured with the treatment strategy used; or 4) CPJI-related death. Mortality was attributed to CPJI if the patient had signs and symptoms of infection at death or microbiologic evidence of active *Candida* infection, and other potential causes of death had been excluded. To evaluate relapse, only patients followed-up for at least 2 years were included in the analysis.

Statistical analysis

Categorical variables are expressed as the absolute frequency and percentage, and continuous variables as the median and interquartile range (IQR). Differences in percentages between groups were assessed by the chi-square test or the Fisher exact test for categorical variables. A 2-tailed *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software, version 22.

Ethics

The study was approved by the Ethics Committee for Clinical Research of Hospital Universitari Vall d'Hebron (PR (AG) 321/2016).

RESULTS

Over the 12-year study period, 57 cases of CPJI were recorded in the participating hospitals. Thirteen were excluded: 12 were spacer infections and 1 was considered a sample contamination and was not treated. In total, 43 patients fulfilled the inclusion criteria.

Patients' baseline and clinical characteristics. Demographic data, comorbid conditions, risk factors predisposing to PJI, site of the arthroplasty, and signs and symptoms at presentation are shown in Table 1. Thirty-four (79.1%) patients had at least 1 risk factor for *Candida* infection. Interestingly, 6 patients had concomitant candidal intertrigo infection and 4 developed CPJI after a previous urinary tract infection caused by the same species of *Candida* (3 patients with documented candidemia, all treated with azoles).

Microbiology. *Candida* species were grown from culture of surgical specimens in 39 patients, joint aspirate in 18, and percutaneous joint biopsy in 7 (some patients had samples from more than 1 site). The species most commonly found were *C. albicans* and *C. parapsilosis*, and a coexisting bacterial infection was detected in 11 (25.6%) patients (Table 1).

Surgical and medical therapy. Surgical treatment included implant removal in 22 patients and debridement with prosthesis retention in 18. In 3 patients, the infection was discovered in intraoperative cultures on replacement of the prosthesis for other reasons. In the 5 patients who

received an antifungal-impregnated cement spacer, amphotericin B was used in 4 (deoxycholate, 2 and liposomal, 2), and fluconazole in 1. Following surgical treatment, all patients except 1 who died in the early postoperative period received systemic antifungal agents. The medical therapy is summarized in Table 2. Regarding side effects, amphotericin B produced renal impairment in 3 patients and required discontinuation in 1 of them. Fluconazole led to nausea and vomiting in 1, alopecia, cholestasis and rash in 1, and cutaneous vasculitis in the third, requiring discontinuation in all 3 patients. Voriconazole caused hepatotoxicity in 1 patient, flucytosine led to leucopenia in 1, and anidulafungin caused hepatotoxicity in 1; drug withdrawal was not required in any of these 3 patients.

Treatment outcome. Among the 43 patients included, 35 were evaluable for outcome. Six patients died due to a cause unrelated to CPJI before completion of follow-up: 3 patients died during antifungal treatment (1 due to exacerbation of his respiratory disease, 1 due to decompensation of his liver cirrhosis with hepatic encephalopathy, and 1 due to a neurologic event), and 3 patients died within 6 months after completion of treatment (2 due to a cardiac event, and 1 due to *Clostridium difficile* infection after antibiotics use for another indication). One patient was still on treatment, and 1 other required amputation due to a bacterial superinfection during antifungal treatment.

A flowchart summarizing the surgical and medical treatments used in the 35 patients with their respective failure rates is shown in Figure 1. Failure rates in acute and chronic CPJI according to the surgical and medical approaches used are shown in Figure 2.

Overall, 17 of 35 (48.6%) patients cured and 18 of 35 (51.4%) failed treatment. In the comparison of acute versus chronic CPJI, treatment was successful in 4/12 (33.3%) acute cases and 13/23 (56.5%) chronic cases ($p=0.289$). In the comparison of prostheses removal vs. prostheses retention, treatment success rates were 13/20 (67%) for prosthesis removal and 4/15 (26.7%) for debridement with prosthesis retention ($p=0.041$). Of the 20 patients treated with implant removal,

all 3 with an amphotericin B-impregnated cement spacer cured ($p=0.521$). In the prosthesis removal group, 5/6 (83.3%) achieved treatment success with the antibiofilm regimen versus 8/13 (61.5%) with azoles treatment ($p=0.605$) (1 patient did not receive antifungal treatment). Among the debridement and prosthesis retention group, success was 3/10 (30%) for azoles versus 1/5 (20%) for the antibiofilm regimen ($p=1$).

Of the 13 patients who underwent prosthesis removal and had a favorable outcome, a new prosthesis was implanted in 11 patients (7 in 2-stage and 4 in 1-stage exchange surgery) and 2 underwent arthrodesis. Several intraoperative cultures were obtained at the time of reimplantation in all but 1 patient, and all were negative.

Failure was due to relapse in 9 cases, suppressive treatment requirement in 5, persistent infection in 2, and CPJI-related death in 2 (1 due to septic shock in monomicrobial CPJI and 1 due to hypovolemic shock). The 5 patients who received suppressive treatment (all with azoles and 4 without implant removal) showed no adverse effects and maintained good joint functionality. The overall attributable mortality rate was 5.7% (2/35).

Four patients who had failed treatment were retreated and evaluable at 2 years of follow-up. Retreatment consisted of implant removal in all patients (2 delayed reimplantation arthroplasty, 1 direct exchange, and 1 permanent resection arthroplasty). Antifungal therapy with azoles alone was used in 2 patients (1 with a liposomal amphotericin B-impregnated cement spacer), echinocandins sequenced to azoles were used in 1, and echinocandins alone with an amphotericin B deoxycholate - impregnated cement spacer in 1 patient. The infection was eradicated in all cases.

In an overall analysis of the 39 evaluable episodes, including the initial 35 episodes plus those 4 re-treatments, statistically significant differences regarding the surgical approach were also found: success was achieved in 17/24 (70.8%) episodes with implant removal versus 4/15 (26.7%) with implant retention ($p=0.010$). An amphotericin B-impregnated cement spacer was used in 5 of the 24 episodes treated with implant removal, and treatment was successful in all 5 cases. In episodes

treated with prosthesis removal, therapy was successful in 8/9 (88.9%) cases treated with the antibiofilm regimen compared to 9/14 (64.3%) treated with azoles ($p=0.340$).

DISCUSSION

CPJI is a rare condition that poses a therapeutic challenge. In our series, the infection predominantly affected older patients with various comorbid conditions, and nearly 80% had identifiable risk factors for *Candida* infection. CPJI presented mainly as a chronic infection and *C. albicans* was the most common causative microorganism. The treatment used was successful in 49% of patients, whereas 51% failed. Although removal of the implant was the only strategy significantly associated with success, its combination with an antifungal with antibiofilm activity, including an amphotericin B-impregnated cement spacer, achieved higher success rate, which may have reached significance if the sample had been larger.

It is well recognized that CPJI affects older patients with risk factors for *Candida* infection [4,5,14–16,20]. Interestingly, 6 patients in our study had concomitant candidal intertrigo (5 were hip arthroplasties) and 4 had developed a previous urinary tract infection by the same *Candida* species (3 of them were blood-culture positive), factors that are markers of *Candida* colonization. These data suggest that searching and treating candidal intertrigo before hip surgery could be a simple, safe, and inexpensive measure to avoid CPJI. The approach to take in candiduria would be less clear-cut when there are no symptoms, as occurs with asymptomatic bacteriuria [21,22]. It has been reported that hematogenous seeding of a prosthetic joint is a common complication of *Staphylococcus aureus* bacteremia [23], but to our knowledge, the risk of developing CPJI after experiencing candidemia is unknown. It is also uncertain whether treating candidemia with a drug having antibiofilm activity could have an impact on avoiding CPJI.

C. albicans was the most common microorganism isolated, followed by *C. parapsilosis*, which is in accordance with our local epidemiology [24]. The greatest challenge in these patients is the

therapeutic approach, as there is very little guiding evidence and only a few reported case series. Various surgical strategies have been described for CPJI, although the most successful seems to be removal of the implant. A few reports have described successful treatment with retention of the prosthesis, but these infections were treated in the acute stage or had a follow-up shorter than 1 year [25–27]. In chronic infections, irrigation and debridement alone with prosthesis retention has failed to control the infection [4,15]. The success of 1-stage exchange arthroplasty combined with antifungal agents has been reported in only a few cases [28]. In chronic infection, most authors prefer to remove all the infected material, in accordance with the Infectious Diseases Society of America (IDSA) Guidelines [7]; the reported cure rates are very variable (14% to almost 100%) when performing 2-stage exchange arthroplasty [4,5,14,15,20,27]. In our series, treatment was successful in 49% of cases, and implant removal was the surgical strategy significantly associated with a favorable outcome (67% success). The percentage of global success is lower than the 76% recently reported in a review of the related literature [29]. This difference may reflect publication bias of patients with a favorable outcome, the fact that we had a larger number of acute infections, and that 7 chronic infections were treated with debridement and prosthesis retention. Of note, 5 of these 7 infections classified as chronic according to the Tsukayama system occurred during the first 3 months after surgery, and the other 2 were treated with prosthesis retention to avoid an aggressive approach in elderly patients with comorbidities. When cases were divided into acute or chronic, acute infections failed treatment more often, likely because they were usually treated with debridement and prosthesis retention. In contrast to what occurs in bacterial PJI, even acute cases, this strategy had higher failures rates, although the difference was not statistically significant.

As is known, *Candida* spp. grows as a biofilm adhering to medical devices, and this characteristic makes the microorganism highly resistant to antifungal agents and host defense mechanisms [11–13,17]. Azoles and amphotericin-B are the recommended agents for systemic treatment of CPJI [7,20], although fluconazole has been associated with high failure rates [15]. Previous studies have

demonstrated that the activity of azoles against *Candida* spp. biofilms is poor, whereas amphotericin B and echinocandins are both biofilm-active [11,12,17,30–32]. Although echinocandins and amphotericin-B (local or systemic) were used sparingly, the results of our study appear to be promising, with remission rates when combined with implant withdrawal higher than 80% in our series, similar to the values reported in previous studies [16,20,33,34]. Nonetheless, the differences were not statistically significant, probably due to the small number of patients.

The required duration of antifungal treatment also needs clarification. According to previous reports, 6 to 12 months of treatment seemed necessary, particularly when azoles were used [35]. Recent IDSA Guidelines [7] recommend prosthesis removal and at least 3 months of antifungals, but the evidence for this recommendation is low. In 1 small series [33], shorter antifungal courses (eg, 6 weeks) were highly successful when using a 2-stage exchange procedure. In our study, the median duration of antifungal treatment was 3 months, similar to that reported in other series [4,5,14]. Further studies should determine whether treatment duration shorter than 3 months is successful when antibiofilm agents are used, particularly in combination with implant removal. Lastly, in our experience, when prosthesis removal has a very high surgical risk, lengthy suppressive therapy with azoles may be a useful alternative treatment, allowing the (some?) patients to maintain good joint functionality.

It is still controversial whether use of a spacer impregnated with an antifungal agent can improve the prognosis. In staged exchange arthroplasty, fungi may remain adhered to the cement spacer and lead to an infection relapse that is difficult to control. Therefore, antifungal-loaded cement spacers may be a better choice to avert relapse. Nonetheless, there is no consensus on the type or dose of antifungal agent that should be mixed with the cement. Amphotericin B is often used because of its heat stability, broad antifungal spectrum, and availability in powder form. Although amphotericin B-loaded cement spacers have been reported to successfully eradicate CPJI without noticeable nephrotoxicity [16,36,37], there is still some debate about whether the local dose is high enough to

be effective when mixed with cement [11,34,36,38,39]. A recent *in vitro* study showed that release of 800 mg of liposomal amphotericin B was higher than the same dose of deoxycholate amphotericin B when mixed with acrylic bone cement, although it led to a loss of compressive strength [40]. Moreover, as high doses of amphotericin B may be toxic for osteoblasts [41], the *in vivo* bone toxicity of liposomal amphotericin B should be studied before widespread use of the drug for this purpose. In our experience, use of an amphotericin B-impregnated spacer seemed to improve outcome without bone toxicity, but our data did not suffice to determine which type of amphotericin is better.

Certainly, our study has some limitations. One of the major limitations is the small sample, although it is understandable because of the low incidence of CPJI. Nonetheless, the analysis may have been underpowered to detect some significant differences. In addition, it is a non-randomized, retrospective study, so there could be recall bias, and it included patients treated over an extended period, which may have resulted in variability in several factors such as the surgeons, surgical techniques, and antifungal regimens available. Another aspect to mention is that coexisting bacterial infection occurred in around one-quarter of the cases, which could be a confounding factor in the clinical course of these patients. However, it is a multicenter study, carried out in centers with multidisciplinary teams and meticulous recording of data on these patients, and although the sample is small, it is the largest series of its kind published in recent years.

In conclusion, in our experience, CPJI is usually a chronic infection occurring in patients of advanced age, who have several comorbidities and have undergone previous surgeries, which makes application of aggressive surgical treatment more difficult. The success rate is low and treatment with prosthesis removal leads to a better outcome. Amphotericin B and echinocandins seem to be more effective than azoles for eradicating biofilm-embedded *Candida* spp., and although there is insufficient evidence that the use of antibiofilm antifungals has added benefits, our experience indicates that it may be recommendable, particularly in combination with removal of the implant.

Because of the paucity of related information and the complexity of CPJI, we believe it advisable to treat patients with this condition only in experienced, multidisciplinary centers.

FUNDING

This work was supported by Plan Nacional de I+D+i 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0003) - cofinanced by European Development Regional Fund “A way to achieve Europe”, Operative program Intelligent Growth 2014-2020.

CONFLICT OF INTEREST

None.

ACKNOWLEDGEMENTS

We thank Celine Cavallo for English language support.

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REFERENCES

- [1] Kapadia BH, Berg RA, Daley JA, Fritz J, Bhav A, Mont MA. Periprosthetic joint infection. *The Lancet* 2016;387:386–94.
- [2] Cobo J, Del Pozo JL. Prosthetic joint infection: diagnosis and management. *Expert Rev Anti Infect Ther* 2011;9:787–802.
- [3] Tande AJ, Patel R. Prosthetic joint infection. *Clin Microbiol Rev* 2014;27:302–45.
- [4] Azzam K, Parvizi J, Jungkind D, Hanssen A, Fehring T, Springer B, et al. Microbiological, clinical, and surgical features of fungal prosthetic joint infections: a multi-institutional experience. *J Bone Joint Surg Am.* 2009; 91:142–49.
- [5] Phelan DM, Osmon DR, Keating MR, Hanssen AD. Delayed reimplantation arthroplasty for candidal prosthetic joint infection: a report of 4 cases and review of the literature. *Clin Infect Dis* 2002;34:930–38.
- [6] Benito N, Franco M, Ribera A, Soriano A, Rodriguez-Pardo D, Sorlí L, et al. Time trends in the aetiology of prosthetic joint infections: a multicentre cohort study. *Clin Microbiol Infect.* 2016; 22:732.e1-8.
- [7] Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, et al. Diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2013;56:e1–25.
- [8] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016; 62:e1-50.

- [9] Rodríguez-Pardo D, Pigrau C, Corona PS, Almirante B. An update on surgical and antimicrobial therapy for acute periprosthetic joint infection: new challenges for the present and the future. *Expert Rev Anti Infect Ther*. 2015; 13:249–65.
- [10] Ariza J, Cobo J, Baraia-Etxaburu J, Benito N, Bori G, Cabo J, et al. Executive summary of management of prosthetic joint infections. Clinical practice guidelines by the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). *Enferm Infecc Microbiol Clin*. 2017; 35:189–95.
- [11] Kuhn DM, George T, Chandra J, Mukherjee PK, Ghannoum MA. Antifungal susceptibility of *Candida* biofilms: unique efficacy of amphotericin B lipid formulations and echinocandins. *Antimicrob Agents Chemother* 2002; 46:1773–80.
- [12] Nett JE. Future directions for anti-biofilm therapeutics targeting *Candida*. *Expert Rev Anti Infect Ther* 2014;12:375–82.
- [13] Mukherjee PK, Chandra J. *Candida* biofilms: development, architecture, and resistance. *Microbiol Spectr* 2015;3. doi:10.1128/microbiolspec.MB-0020-2015.
- [14] Kuiper JW, van den Bekerom MP, van der Stappen J, Nolte PA, Colen S. 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. *Acta Orthop*. 2013; 84:517–23.
- [15] García-Oltra E, García-Ramiro S, Martínez Pastor JC, et al. Prosthetic joint infection by *Candida* spp. *Rev Esp Quimioter*. 2011; 24:37-41.
- [16] Ueng SWN, Lee CY, Hu C, Hsieh PH, Chang Y. What is the success of treatment of hip and knee candidal periprosthetic joint infection? *Clin Orthop Relat Res*. 2013; 471:3002–9.

- [17] Iñigo M, Pemán J, Del Pozo JL. Antifungal activity against *Candida* biofilms. *Int J Artif Organs*. 2012; 35:780-91.
- [18] Tsukayama DT, Estrada R, Gustilo RB. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. *J Bone Joint Surg Am*. 1996; 78:512–23.
- [19] Segawa H, Tsukayama DT, Kyle RF, Becker DA, Gustilo RB. Infection after total knee arthroplasty. A retrospective study of the treatment of eighty-one infections. *J Bone Joint Surg Am*. 1999; 81:1434–45.
- [20] Hwang BH, Yoon JY, Nam CH, Jung KA, Lee SC, Han CD, et al. Fungal peri-prosthetic joint infection after primary total knee replacement. *J Bone Joint Surg Br*. 2012; 94:656–9.
- [21] Cordero-Ampuero J, González-Fernández E, Martínez-Vélez D, Esteban J. Are antibiotics necessary in hip arthroplasty with asymptomatic bacteriuria? Seeding risk with/without treatment. *Clin Orthop*. 2013; 471:3822–9.
- [22] Honkanen M, Jämsen E, Karppelin M, Huttunen R, Huhtala H, Eskelinen A, et al. The impact of preoperative bacteriuria on the risk of periprosthetic joint infection after primary knee or hip replacement: a retrospective study with a one-year follow-up. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2017. doi:10.1016/j.cmi.2017.07.022.
- [23] Murdoch DR, Roberts SA, Fowler Jr VG, Shah MA, Taylor SL, Morris AJ, et al. Infection of orthopedic prostheses after *Staphylococcus aureus* bacteremia. *Clin Infect Dis* 2001;32:647–9.
- [24] Puig-Asensio M, Padilla B, Garnacho-Montero J, Zaragoza O, Aguado JM, Zaragoza R, et al. Epidemiology and predictive factors for early and late mortality in *Candida* bloodstream infections: a population-based surveillance in Spain. *Clin Microbiol Infect*. 2014; 20:245–54.

- [25] Fukasawa N, Shirakura K. *Candida* arthritis after total knee arthroplasty-a case of successful treatment without prosthesis removal. *Acta Orthop Scand*. 1997; 68:306–7.
- [26] Merrer J, Dupont B, Nieszkowska A, De Jonghe B, Outin H. *Candida albicans* prosthetic arthritis treated with fluconazole alone. *J Infect*. 2001; 42:208–9.
- [27] Brooks DH, Puppato F. Successful salvage of a primary total knee arthroplasty infected with *Candida parapsilosis*. *J Arthroplasty* 1998; 13:707–12.
- [28] Selmon GPF, Slater RNS, Shepperd JN, Wright EP. Successful 1-stage exchange total knee arthroplasty for fungal infection. *J Arthroplasty* 1998; 13:114–5.
- [29] Cobo F, Rodríguez-Granger J, Sampedro A, Aliaga-Martínez L, Navarro-Marí JM. *Candida* prosthetic joint infection. A review of treatment methods. *J Bone Jt Infect*. 2017; 2:114–21.
- [30] Katragkou A, Chatzimoschou A, Simitsopoulou M, Dalakiouridou M, Diza-Mataftsi E, Tsantali C, et al. Differential activities of newer antifungal agents against *Candida albicans* and *Candida parapsilosis* biofilms. *Antimicrob Agents Chemother* 2008;52:357–60.
- [31] Bartalesi F, Fallani S, Salomoni E, Marcucci M, Meli M, Pecile P, et al. *Candida glabrata* prosthetic hip infection. *Am J Orthop Belle Mead NJ* 2012;41:500–5.
- [32] Graw B, Woolson S, Huddleston JI. *Candida* infection in total knee arthroplasty with successful reimplantation. *J Knee Surg* 2010;23:169–74.
- [33] Anagnostakos K, Kelm J, Schmitt E, Jung J. Fungal periprosthetic hip and knee joint infections. *J Arthroplasty* 2012; 27:293–8.
- [34] Schoof B, Jakobs O, Schmidl S, Klatte TO, Frommelt L, Gehrke T, et al. Fungal periprosthetic joint infection of the hip: a systematic review. *Orthop Rev* 2015; 7:5748.

- [35] Aguado JM, Ruiz-Camps I, Munoz P, Mensa J, Almirante B, Vázquez L, et al. Guidelines for the treatment of invasive candidiasis and other yeasts. Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC). 2010 Update. *Enferm Infecc Microbiol Clin*. 2011; 29:345–361.
- [36] Marra F, Robbins GM, Masri BA, Duncan C, Wasan KM, Kwong EH, et al. Amphotericin B-loaded bone cement to treat osteomyelitis caused by *Candida albicans*. *Can J Surg*. 2001; 44:383.
- [37] Deelstra JJ, Neut D, Jutte PC. Successful treatment of *Candida albicans*-infected total hip prosthesis with staged procedure using an antifungal-loaded cement spacer. *J Arthroplasty*. 2013; 28:374.e5-374.e8.
- [38] Goss B, Lutton C, Weinrauch P, Jabur M, Gillett G, Crawford R. Elution and mechanical properties of antifungal bone cement. *J Arthroplasty*. 2007; 22:902–8.
- [39] Kweon C, McLaren AC, Leon C, McLemore R. Amphotericin B delivery from bone cement increases with porosity but strength decreases. *Clin Orthop Relat Res*. 2011; 469:3002-7.
- [40] Cunningham B, McLaren AC, Pauken C, McLemore R. Liposomal formulation increases local delivery of amphotericin from bone cement: a pilot study. *Clin Orthop Relat Res*. 2012; 470:2671–6.
- [41] Harmsen S, McLaren AC, Pauken C, McLemore R. Amphotericin B is cytotoxic at locally delivered concentrations. *Clin Orthop Relat Res*. 2011; 469:3016–3021.

Table 1. Baseline characteristics, clinical and microbiological features of 43 patients diagnosed with *Candida* periprosthetic joint infection

Features	N (%)
Sex , women/men	33 (76.7)/10 (23.3)
Age , years	75 (69-80)
Age-adjusted Charlson Comorbidity Index score	4 (3-5)
Comorbidities	
- Diabetes mellitus	13 (30.2)
- Chronic renal failure	7 (16.3)
- Immunosuppressive therapy	6 (14)
- Rheumatoid arthritis	5 (11.6)
- Malignancy	2 (4.7)
- Liver cirrhosis	2 (4.7)
Other risk factors for <i>Candida</i> infection	
- Revision prosthesis	21 (48.8)
- Antibiotics for ≥ 14 days during the previous 3 months	20 (46.5)
- Previous surgeries involving the current prosthesis	11 (25.6)
- Previous <i>Candida</i> infection in another location	10 (23.3)
Site of arthroplasty	
- Hip	26 (60.5)
- Knee	16 (37.2)
- Shoulder	1 (2.3)
Tsakayama classification [18]	
- Late chronic periprosthetic joint infection	25 (58.1)

- Early post-surgery periprosthetic joint infection	12 (27.9)
- Hematogenous periprosthetic joint infection	3 (7)
- Positive intraoperative cultures	3 (7)
Clinical manifestations*	
- Pain	31/40 (77.5)
- Inflammatory signs (effusion, erythema or warmth around the joint)	26/40 (65)
- Purulent exudates	13/40 (32.5)
- Fever	8/40 (20)
- Fistula	8/40 (20)
Implant loosening on radiography	21 (48.8)
Blood leukocytes count, cells/mm³	8300 (7200-10400)
C-reactive protein value, mg/dL	3.8 (1.7-8.8)
Erythrocyte sedimentation rate, mm/h	66 (51-90)
Joint fluid white cell count, cells/mm³, and neutrophil differential, %	9750 (6400-21425), 85 (68-95)
Microbiology results	
- <i>C. albicans</i>	24 (54.8)
- <i>C. parapsilosis</i>	14 (32.6)
- <i>C. glabrata</i>	2 (4.7)
- <i>C. tropicalis</i>	1 (2.3)
- <i>C. albicans</i> and <i>C. parapsilosis</i>	1 (2.3)
- <i>C. parapsilosis</i> and <i>C. tropicalis</i>	1 (2.3)
- Coexisting bacterial infection**	11 (25.6)

Categorical variables are expressed as the absolute number and percentage, and continuous variables as the median and interquartile range (IQR)

*Patients may have more than one clinical manifestation

**Polymicrobial infection in 4 patients, coagulase-negative *Staphylococcus* in 3, *Staphylococcus aureus* in 2, and *Corynebacterium spp.* in 2

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Table 2. Summary of medical treatment of the 42 patients with *Candida* periprosthetic joint infection who received antifungal therapy

Antifungal therapy	Number of patients	Total duration, days	Percentage of total treatment time during which each antifungal was administered
Azoles	26	118 (65-181)	Azoles 100%
Echinocandins* and azoles	7	102 (92-162)	Echinocandins 34% (24-46), azoles 73% (54-95)
Systemic amphotericin B and azoles	2	225 (90 and 360)	Amphotericin B 26% (25% and 28%), azoles 74% (72 and 75)
Echinocandins*	1	57	Echinocandins 100%
Echinocandins*, flucytosine, and azoles	1	182	Echinocandins 86%, flucytosine 50%, azoles 41%
Chronic suppressive therapy with azoles**	5	3 patients initially received echinocandins* (15, 15, and 30 days) and 1 amphotericin B (15 days).	

Continuous variables are expressed as the median and interquartile range (IQR).

*Echinocandins used were anidulafungin in 6 patients, caspofungin in 5, and micafungin in 1.

**Suppressive treatment with fluconazol 200mg/day was given in 5 patients in whom it was considered that the treatment strategy used would not cure the infection (4 treated with implant retention and 1 with resection arthroplasty). After a median follow-up of 16.5 (14.3-36.7) months, none had to stop treatment due to adverse events, and all maintained good joint functionality.

Figure 1. Flowchart of failure rates according to the medical and surgical approaches used

*Echinocandins or local or systemic amphotericin B

Figure 2. Flowchart of failure rates in acute (early) and chronic (late) CPJI depending on the surgical and medical approach used

*Echinocandins or local or systemic amphotericin B