

# Fungal periprosthetic joint infection of the hip: a systematic review

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## Abstract

Periprosthetic joint infection (PJI) is a severe complication of total joint arthroplasty with an incidence of approximately 1%. Due to the high risk of persisting infection, successful treatment of fungal PJI is challenging. The purpose of this study was to gain insight into the current management of fungal PJI of the hip and, by systematically reviewing the cases published so far, to further improve the medical treatment of this serious complication of total hip arthroplasty. Thus, we conducted a systematic review of the available literature concerning fungal PJI in total hip arthroplasty, including 45 cases of fungal PJI. At the moment a two-stage revision procedure is favorable and there is an ongoing discussion on the therapeutic effect of antifungal drug loaded cement spacers on fungal periprosthetic infections of the hip. Due to the fact that there is rare experience with it, there is urgent need to establish guidelines for the treatment of fungal infections of total hip arthroplasty.

## Introduction

Periprosthetic joint infection (PJI) is a severe complication of total joint arthroplasty with an incidence of approximately 1%.<sup>1</sup> Several studies have demonstrated that coagulase-negative staphylococci and *Staphylococcus aureus* account for approximately 50% of all PJI cases.<sup>2-6</sup> Furthermore, fungal periprosthetic joint infection, which constitutes about 1% of all PJI,<sup>7</sup> is rarely reported in the literature.

Multiple potential risk factors for the development of fungal PJI, like immunosuppression, neutropenia, and chronic or prolonged use of antibiotics, have been identified.<sup>2,7-11</sup> As

Brooks *et al.* showed in 1998, at least one of these relevant risk factors was identified in approximately one-half of the reported cases of fungal PJI.<sup>2</sup> Due to a high risk of persisting infection, successful treatment of fungal PJI is challenging. Currently, 45 cases of fungal PJI of the hip have been reported. The infection was controlled in only 16 of these cases.<sup>8,12-15</sup>

As for the optimal treatment of fungal PJI of the hip, no standardized guidelines have been developed so far. This fact explains the broad range of antimicrobial and surgical treatment protocols in the current published cases of fungal PJI of the hip.<sup>2,8,9,13,16-18</sup>

The purpose of this study was to gain insight into the current management of fungal PJI of the hip and, by systematically reviewing the currently published cases, to further improve the medical treatment of this serious complication of total hip arthroplasty.

## Materials and Methods

We conducted a systematic review of the available literature using various search strategies. The databases (Medline, PubMed, Embase, and Scopus) were searched using the terms *arthroplasty*, *hip*, *infection*, and *fungal*. To ensure accuracy, repeated searches were performed between 10 March 2013 and 20 March 2013. No additional studies were identified by repeating the search. Title, abstract, and the full text were reviewed when they were identified as relevant by the aforementioned database searches. To identify any important reports that had been missed during the initial search, a manual search of the references from the selected papers was also performed. A meta-analysis was not performed due to the heterogeneity of the studies as well as the high amount of case reports and case series.

The following data were extracted from the studies: demographics (including age, gender, and body mass index), smoking habits, concomitant diseases (especially immunocompromising risk factors such as diabetes mellitus, corticosteroid therapy, malignant disease, and organ transplantation), and prolonged antibiotic treatment. Data were recorded using Microsoft Excel 2007 (Microsoft Corporation, Redmond, Washington) and analyzed using SPSS software, v15.0 for Windows (SPSS Inc, Chicago, IL, USA).

## Results

### Study population

Our search yielded 21 publications including 45 cases of fungal PJI of the hip. The included studies and patients are given in Table 1.<sup>19-38</sup> The mean age of the patients at

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diagnosis was 69 years. There were 26 female (58%) and 19 male (42%) patients. Obesity was recorded in 2 cases, nicotine abuse in 1 case, and alcohol abuse in 3 cases.

### Concomitant diseases

Concomitant diseases, according to the risk factors for invasive fungal infections, were reported in 66% of the cases as presented in Figure 1A. No prior concomitant diseases were reported prior for 16% of patients. On the other hand, rheumatoid arthritis, diabetes mellitus and previous cases of bacterial PJI were frequently shown in the cohort.

### Preoperative findings

Leading clinical symptoms shown at presentation included pain in 23 patients (51%), local signs of infection (such as erythema, swelling, and local warmth) in 37 (84%), and signs of systemic infection (such as fever and nightly sweats) in 5 patients (11%). Elevated serological infection parameters (WBC, ESR, or CRP) were reported in 23 cases. Due to insufficient data regarding the standard values and the reported parameters, a detailed analysis was not necessary.

Radiological evaluation of the prosthesis was reported in 53% of the studies. The most common finding was a loosening of the prosthesis (51%) followed by regional osteolysis or bone destruction (2%). In 5% of the cases, radiological analysis did not reveal any suspicious pathology and a radiological analysis was not included in 42% of the cases.

Preoperative joint aspiration was performed in 19 cases (42%). In 9 of the analyzed studies

the authors reported microbiological details about the number of cultures, but none of the authors reported on the growth medium or the time of incubation. *Candida* species [mainly *Candida albicans* (54%), followed by *Candida parapsilosis*, *glabrata*, and *tropicalis*] have been found to be pathogenic in 84% of patients (Figure 1B). No preference could be observed regarding all other fungal specimens, bearing in mind that these cases represent a mere 1% of all PJI cases.<sup>7</sup>

### Surgical treatment

Within the whole series of the reviewed 45 cases of fungal PJI of the hip, the surgical treatment protocols (Figure 1C) included 7 permanent resection arthroplasties (16%), 2 direct exchanges (4%, one-stage-procedure), 26 delayed reimplantation arthroplasties (58%),

two-stage-procedure), 1 delayed arthrodesis (2%), 5 debridements with retention of the prosthesis (11%), and 4 cases treated by a medicamentous suppression therapy with an antimycotic agent (9%). In most of the studies, an extensive and radical intraoperative debridement of all infected and necrotic tissue was emphasized as highly important. In the cases of implant exchange, this included the thorough removal of all cement.

In 8 cases, a resection arthroplasty was performed as an initial surgical intervention to control the infection without reimplantation of a THA (Girdlestone procedure).

The application of intraarticular spacers was very heterogeneous in staged revision procedures. Intraarticular spacers had been used in 10 patients of which 4 had been treated with topical antifungal agents. In 11 cases, no spacer

was implanted following removal of the prosthesis by means of a temporary Girdlestone procedure.

In 2 cases (4%) without pre- or intraoperative suspicion of a periprosthetic infection a one-stage-procedure was performed and successfully controlled the infection.

Debridement and irrigation with retention of the prosthesis was implemented in 11% of the cases with 1 patient receiving an arthrodesis after 8 weeks of systemic treatment with Amphotericin B.

In 11 cases (24%) the fungal PJI of the hip was not controlled. Out of these cases 3 cases presented clinical signs of infection (such as persisting wound effusion and swelling), 5 cases required suppressive therapy with fluconazole (400 mg/d), and 3 cases presented a recurrence of the PJI.

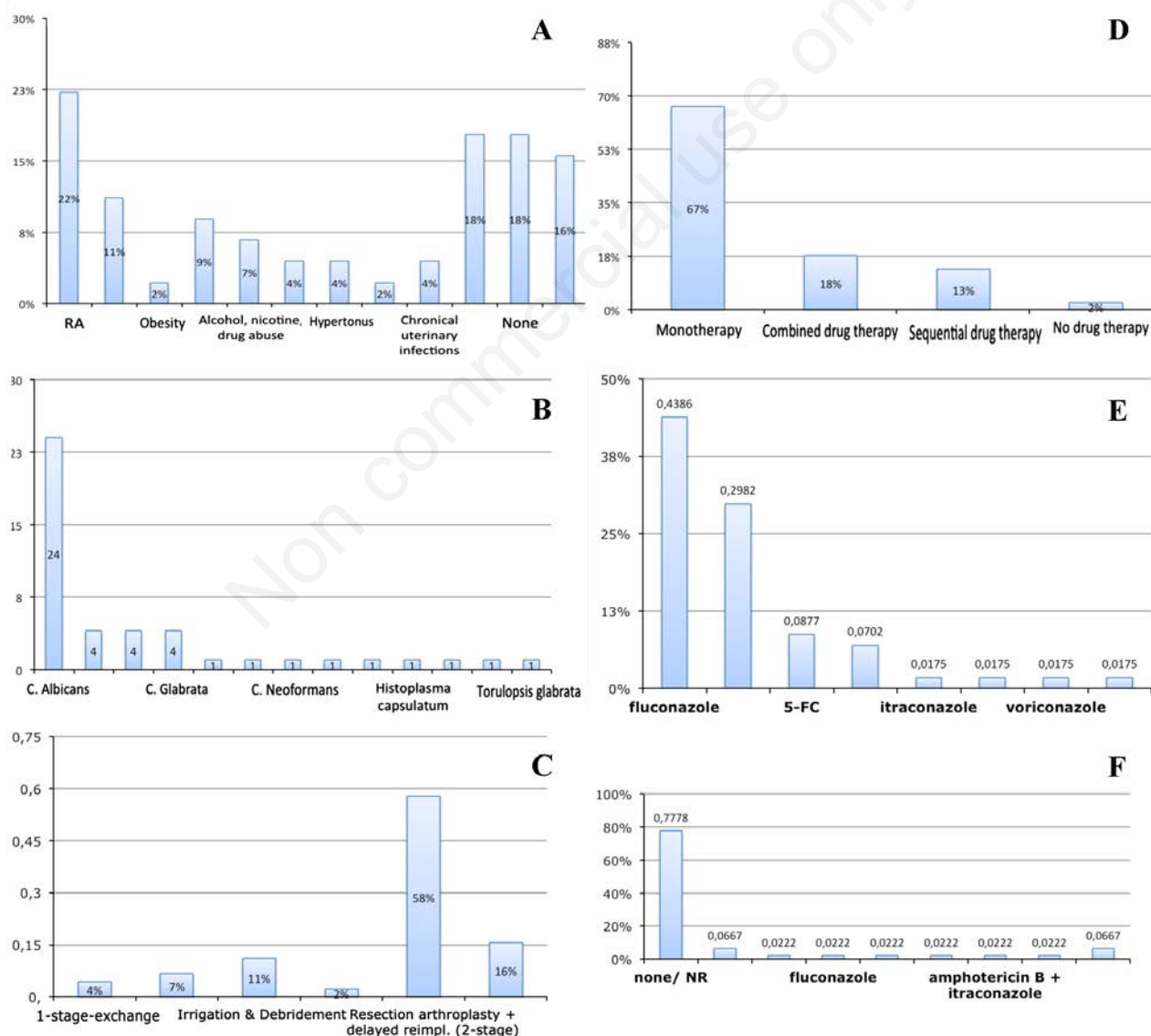


Figure 1. A) Concomitant diseases (in %); B) spectrum of pathogens in the 45 reported cases of fungal PJI; C) surgical treatment protocols; D) medicamentous therapy concept; E) administration of antimycotic/antibacterial agents (%); F) locally administered agents (%).

## Medical therapy

Figure 1D shows that the favored antimicrobial treatment was a monotherapy. Fluconazole was used in 44% of cases and amphotericin B in 30% of the cases (Figure 1E). In selected cases, 5-flucytosine, caspofungin, itraconazole, voriconazole and ketoconazole were also used. In 5 cases, vancomycin was administered additionally, including 1 case switching to methicillin. In one other case, cephazoline and ciprofloxacin were administered additionally.

In Figure 1F, topical drug therapy is graphically demonstrated. In 35 cases (78%) there was no use of a topical antifungal agent.

## Outcome

The follow-up interval was reported in 32 of the 45 cases at a mean interval of 36 months (range: 2 to 73 month). In 10 cases successful revision was supported by normalizing serological values as well as normal radiological and clinical signs. In 9 cases it was stated that patients felt *well* at latest follow-up. In 12 cases no clinical outcome was reported and 5 of the reported patients died due to other causes. In 8 cases (18%) the authors reported a persistent fungal infection or a transition to a bacterial PJI. The studies did not evaluate hip joint function in any of the most recent follow-ups.

In cases of a two-stage-revision procedure, a reinfection rate of 23% (6/26 cases) was documented. In this group, 35% of the patients (9/26 cases) were cured, 5 patients died due to unrelated causes, and no outcome data was available for 6 patients.

Permanent resection arthroplasty led to a reinfection rate of 14% (1/7 cases). Patients treated with irrigation and debridement alone showed a reinfection rate of 67% (4/6 cases). The patients treated with resection arthroplasty followed by arthrodesis and the 2 patients treated by a one-stage procedure showed no signs of reinfection at latest follow-up. 2 patients treated with a medicamentous antifungal suppression therapy (fluconazole) showed signs of reinfection such as persisting effusion and swelling.

## Discussion and Conclusions

To the best of our knowledge, there is no consensus regarding diagnosis and treatment of fungal PJI and there are also no guidelines or even general recommendations for treating fungal PJI. Based on growing numbers of THA, bacterial PJI is projected to increase as well. Currently, fungal PJI is rare with an estimated incidence of approximately 1% of all PJI, but it can be presumed that the incidence of fungal

PJI will also increase.<sup>7,26,39</sup>

The popular opinion that concomitant diseases instigate a fungal PJI was confirmed by our study. On the other hand concomitant diseases such as immunodeficiency, diabetes mellitus or rheumatoid arthritis do not only instigate a fungal PJI but they also hinder the successful treatment of this devastating complication of hip arthroplasty.<sup>40-42</sup> In addition some authors describe a general phenomenon of coexisting or disproportionate history of bacterial PJI in fungal PJI.<sup>40,41</sup> Our findings present similar results identifying 11 patients (24.4%) with previous bacterial PJI or bacteremia due to another cause.

## Surgical treatment

As identified in our study, authors of the current literature actually favor a two-stage revision procedure to treat a fungal PJI with (8/45) and without (19/45) the use of cement spacers. Based on the 21 studies included to this review (Table 1), 77.3% of the infections could be controlled with this staged treatment strategy.

The alternative to the two-stage revision is the single-stage exchange which was described twice in fungal PJIs of the hip by Darouiche in 1989 and Cardinal in 1996 with a short follow up of only 6 and 8 months.<sup>7,9,26</sup> These 2 one-stage revisions of fungal PJIs of the hips were successfully controlled but a longer clinical follow-up is missing in these cases. Other treatment protocols were associated with high reinfection rates. Permanent resection arthroplasty was performed in 8 of the 45 reported cases and turned out to only control 50% of the infections.<sup>38-43</sup> In a multicenter study Azzam *et al.* recently demonstrated that debridement of the joint alone without removal of the implant or initiation of an antibiotic therapy was associated with a reinfection rate of approximately 75% (5/7

cases).<sup>40</sup> In this context, one clearly has to state that the two-stage revision procedure should be considered the *gold standard* in the treatment of fungal PJI.

## Medical therapy

A controversial issue in the treatment of fungal PJI is the appropriate agent as well as duration of antimicrobial therapy. Review of the reported cases on fungal PJI shows that there is a broad variety regarding the duration

**Table 1. Studies included in this review.**

First author	Year	Patients
Anagnostakos <sup>19</sup>	2012	4
Cardinal <sup>20</sup>	1996	3
Cutrona <sup>21</sup>	2002	1
Darouiche <sup>7</sup>	1989	3
Dutronic <sup>22</sup>	2010	3
Evans <sup>23</sup>	1990	2
Fowler <sup>24</sup>	1998	1
García-Oltra <sup>25</sup>	2011	9
Goodman <sup>26</sup>	1983	1
Gottesman-Yekutieli <sup>27</sup>	2011	1
Hall <sup>28</sup>	2012	1
Johannsson <sup>29</sup>	2009	1
Kelesidis <sup>30</sup>	2010	1
Lambertus <sup>31</sup>	1988	1
Lazzarini <sup>32</sup>	2004	1
Marra <sup>33</sup>	2001	1
Merrer <sup>34</sup>	2001	1
Nayeri <sup>35</sup>	1997	1
Phelan <sup>36</sup>	2002	6
Ramamohan <sup>37</sup>	2001	1
Younkin <sup>38</sup>	1984	1

**Table 2. Therapy concepts and duration.**

Drugs	Dose	Pre-explantation	Preoperative	Postoperative	Oral/intravenous
Fluconazole	400 mg 2x/d		3 weeks	6 weeks	Oral
Fluconazole	200 mg/d		7 weeks		Oral
Amphotericin B	15 mg/kg daily, max.1 g		10 weeks		
Fluconazole	400 mg/d		38 weeks		
Amphotericin B	35 mg/kg daily, max 1.45 g		6 weeks		Oral
Fluconazole	400 mg/d		4 weeks	4 weeks	Oral
Amphotericin B	1 mg/kg i.v.		4 weeks		Intravenous
Caspofungin	-	1 week			
Fluconazole	-	6 weeks	6 weeks		
Fluconazole	800/400 mg/d		6 weeks		
Caspofungin	70/50 mg/d		6 weeks		
Voriconazole	800/400 mg/d		6 weeks		



of perioperative systemic antimicrobial agent administration. Well-established agents for a systemic treatment are fluconazole (400-800 mg daily) and amphotericin B (15-35 mg daily) given either orally or intravenous (Table 2).

In staged-revision procedures, Hwang proposed the administration of antifungal agents (such as amphotericin B and fluconazole) depending on the specific fungal species for at least 6 weeks, until reimplantation of the prosthesis is performed. In his study the mean duration until reimplantation was 9.5 weeks (range 6 to 24 weeks).<sup>42</sup> In addition, Hwang stated that oral antibiotics should be administered for a maximum of 6 months after reimplantation.

Anagnostakos *et al.* administered antibiotics for a minimum of 6 weeks. The mean spacer implantation time was 12 weeks (12 to 14 weeks).<sup>41</sup> Azzam described a minimum antibiotic treatment length of 6 weeks and an additional 6 month treatment with fluconazole after reimplantation.<sup>40</sup>

### Spacers

Even though the majority of reports from the last decade describe the use of spacers loaded with antifungal agents supporting the treatment of fungal PJI, there is controversy regarding the type and dose of antifungal agents added to the spacer.<sup>16,20,32,35</sup>

Since amphotericin B is heat stable and available in powder form it is frequently used as an antifungal agent in cement spacers. *In vivo* studies by Marra *et al.* in 2001 showed that an amphotericin B serum level of 1.2 mg/L was detected at 6 hours after surgery and serum concentrations were undetectable after 2 days; 3.2 mg/L maximum found fluid concentration at 2 days after implantation were measured by high-pressure liquid chromatography when 700 mg amphotericin B was mixed with 4 mixes of Palacos bone cement (Smith & Nephew, Richards, Memphis, TN, USA).<sup>44</sup>

Harmsen *et al.* showed that amphotericin B is lethal to osteoblasts and fibroblasts at concentrations of 100 mg/L and above and sublethally cytotoxic at 5 and 10 mg/L. The authors of the study suggest that the high concentrations of amphotericin B needed to overcome suppressed susceptibility of fungi in biofilms could be locally toxic and impact the surgical wound healing site.<sup>45</sup> The use of antibiotic spacers without antifungal drugs in the treatment of fungal PJI may play a role in the prevention of bacterial superinfection.<sup>19</sup>

Some recent *in vitro* studies document a very good elution of voriconazole from PMMA and activity on bioassay, but its presence in bone cement leads to expense of compressive strength.<sup>46</sup> It is now being questioned whether dose of antifungal drugs in bone cement is high enough to destroy fungal biofilms.<sup>44,45</sup>

Facing the fact that fungal PJI presents a

serious increasing problem in arthroplastic surgery of the hip, there is an urgent need to establish guidelines for the treatment of fungal periprosthetic infections of hip.

Due to fact that there is rare experience with fungal infections of THA, revision surgery should be performed in experienced centers only. Before revision surgery it is absolutely necessary to create optimal conditions including preparation of the patient pre-, peri- and postoperatively, meaning nutrition, concomitant diseases, choice of revision prosthesis models and the choice of antifungal and antibiotic drugs.

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