MENTORS IN ORTHOPEDICS

APPROACHES IN SURGICAL TREATMENT OF FUNGAL PROSTHETIC JOINT INFECTION

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SUMMARY

Background: Fungal prosthetic joint infection (fPJI) is an infrequent but complex complication of arthroplasty, occurring in 0.6% to 2% of cases. Primarily caused by Candida species, these infections are characterized by insidious clinical presentations and the formation of resilient biofilms on prosthetic surfaces. Diagnosis is often delayed due to non-specific inflammatory markers and the requirement for prolonged culture incubation.

Objective: This review synthesizes current literature regarding the epidemiology, risk factors, diagnostic protocols, and surgical management strategies for fPJI to provide evidence-based clinical recommendations.

Key Points: Candida species account for 50% to 80% of cases, frequently involving polymicrobial biofilms with Staphylococcus species. Risk factors include immunosuppression, diabetes, and prior revision surgery. Diagnostic accuracy relies on standardized sampling, as systemic markers like C-reactive protein may remain normal. Surgical options include debridement, antibiotics, and implant retention (DAIR), which demonstrates low success rates (20-30%), and staged revision. Two-stage revision is the most utilized approach, with reported success rates between 47% and 100%. Emerging protocols suggest three-stage revisions or antifungal-loaded spacers containing amphotericin B or voriconazole. However, optimal antifungal duration and reimplantation timing remain controversial.

Conclusion: Management of fPJI requires aggressive surgical debridement combined with prolonged systemic antifungal therapy. While two-stage revision is the current preferred strategy, the lack of high-level evidence necessitates multicenter studies to standardize treatment algorithms and optimize local antifungal delivery methods.

KEYWORDS

Prosthesis-Related Infections; Arthroplasty, Replacement, Knee; Arthroplasty, Replacement, Hip; Mycoses; Antifungal Agents

INTRODUCTION

Among the many thousands of species of fungi, about a 100-cause infection in h umans [1]. Fungal infections are not readily recognized and do not advertise their presence and are not easy to demonstrate [2],[3]. Fungal arthritis has a worldwide distribution with prevalence ranging from 0.4% to 20%, is more in men and usually presents as oligoarthritic [2]. Fungal prosthetic joint infection (fPJI) ranges between 0.6-2% [4],[5]. Bone and joint fungal infection may result from direct inoculation, contiguous spread, or hematogenous seeding, which is the most common, and more commonly causes osteomyelitis than septic arthritis. [1],[6],[7]. There are conflicting reports on the common age and commonest sex affected by fPJI, with a range between 52 and 85 years and some reports of male predominance and others of female predominance [5],[8],[9].

The course of fPJI is both insidious and indolent. Clinical symptoms and signs are variable, but pain, swelling and sinus tract are the most common, and are reported in 75-100%, 25-73% and 0-80% of cases respectively [4],[5],[9], [10]. Other variable presentations are low grade fever, reduced range of motion, warmth, and redness. There is poor evidence in literature regarding the management of fPJI and the main guidelines are based on case reports, case series, reviews, and expert opinion [4],[5],[11],[12],[13],[14]. Other sources are the consensus of opinions at different infection societies. We have reviewed the literature and the available knowledge (PubMed, Google Scholar, Orth Evidence, book chapters and infection societies consensus) and came out with recommendations based on the best consistency opinion of experts and infection societies [15],[14],[16],[17],[18].

RESULTS

Fungal PJI is most commonly caused by the Candida Albicans and non -Albicans species (50-80%), followed by Aspergillus [19],[20],[21],[22].

A major factor of the virulence of Candida is its ability to form biofilms, attaching to biotic and abiotic substrates, and forming on synthetic polymers as prosthetic plastics, which are hard to eradicate and are resistant to conventional antifungal treatments [9],[23]. Candida Albicans produces larger and more complex biofilm than other Candida species [9], hence it is recommended to remove the device affected, and the biofilm formation passes through 4 stages; i) adsorption and adhesion of C. albicans yeast cells to a substrate, ii) formation of microcolonies and production of extracellular matrix, iii) maturation and iv) dispersal of cells from the mature biofilm, (Fig. 1) [23]. Once formed, the biofilm is highly tolerant to antifungal therapy and can serve as a reservoir for recurrent infection.

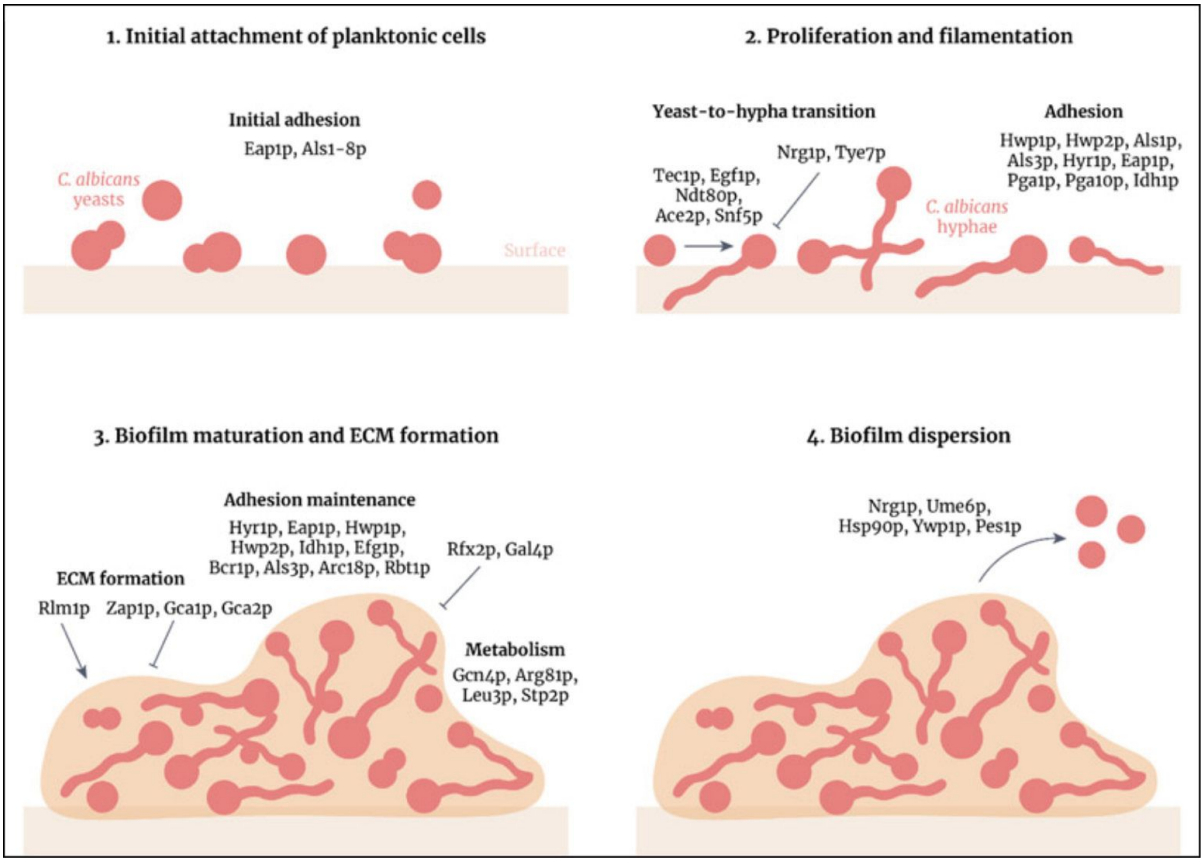

Figure 1: Stages of Candida albicans biofilm formation and development. Candida albicans biofilm formation is a multifactorial process that consists of four main stages. 1) Initial attachment of planktonic cells: C. albicans yeasts attach to a surface (e.g. epithelia, biomaterials or cellular aggregates) through adhesins. 2) Proliferation and filamentation: yeasts transition to hyphae and this process is regulated by many transcription factors 3) Biofilm maturation and extracellular matrix formation: the matrix forms around the C. albicans cells, positively regulated by the TF Rlm1p, providing structural support and protection against antifungals and the host immune system. Adhesion is maintained and amino acid metabolism is increased in the biofilm. 4) Biofilm dispersion: yeast cells disperse from the biofilm to colonise other parts of the body. These cells differ from initial planktonic cells as they are more virulent and more likely to form biofilms. Reprinted from open access reference (23)

It is a common occurrence to have a concomitant bacterial infection among cases of fPJI, ranging between 16%-66%, most commonly Staphylococcus species followed by streptococcus spp. [4],[7],[21],[24]. This wide range of bacterial co-infection could be because the reported cases in literature included primary arthroplasty, re-explored knee joints, revision, and re-revision arthroplasty cases.

One other factor which may explain the high concomitant bacterial infection is the interactions of C. albicans with other microorganisms which can occur via co-aggregation and co-adhesion. C. albicans adhesins facilitate interaction with bacterial species such as Streptococcus gordonii and Staphylococcus aureus, (Fig. 2)[23].

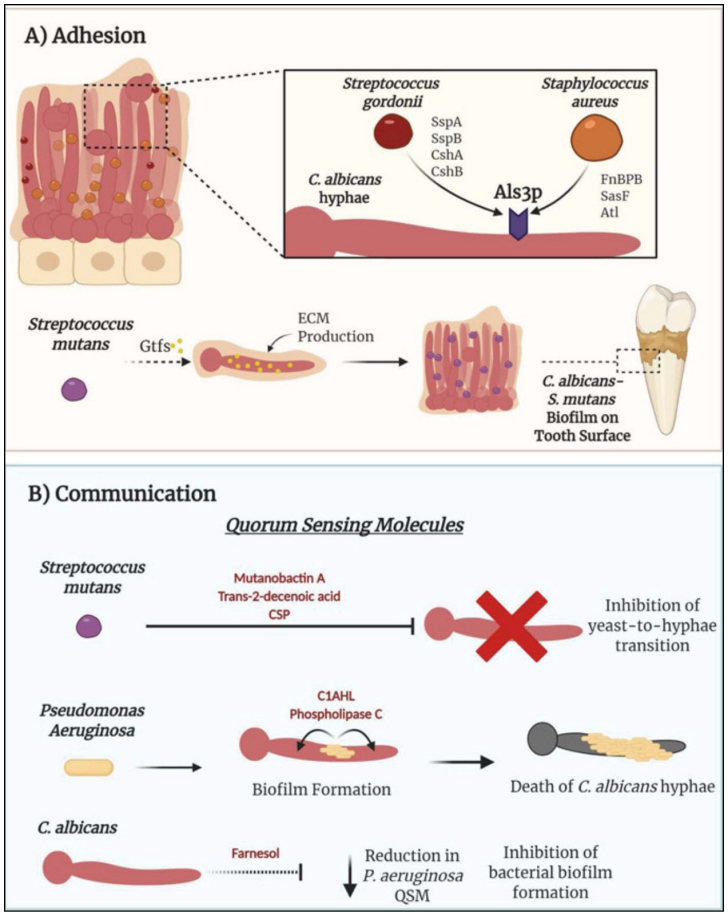

Figure 2: C. albicans interactions within a multispecies biofilm. Complex physical and chemical interactions govern the development of polymicrobial biofilms. A) Several factors influence C. albicans-bacterial adhesion. Staphylococcus aureus and Streptococcus gordonii can utilise C. albicans adhesins to directly bind to hyphae. In contrast, glycosyltransferases (Gtfs) secreted by Streptococcus mutans within the oral cavity can bind to C. albicans mannans, increasing the production of glucans and ECM production. Consequently, the glucan increases the ability of the bacterium to bind to C. albicans and forms a C. albicans-S. mutans biofilm on the tooth surface (dental plaque). B) Signalling molecules produced by C. albicans and bacterial species enable interkingdom communication within multispecies biofilms. For example, S. mutans and Pseudomonas aeruginosa can secrete quorum sensing molecules that influence the behaviour of C. albicans within the biofilm. Likewise, the C. albicans quorum sensing molecule farnesol, can influence the behaviour of interacting bacteria. Reprinted from open access reference (23)

There are several risk factors reported in literature. Fungal PJI occurs most commonly in immune compromised patients, those with previous surgeries and revision cases of joint replacement. Riaz et al. [4],[22] reported that antimicrobial therapy within three months before the diagnosis of PJI and the presence of wound drainage lasting longer than five days prior to the diagnosis of PJI are independent risk factors and significantly associated with increased odds of fPJI when compared with bacterial PJI. Other risk factors of fPJI include diabetes, prolonged use of antibiotics, previous PJI and immunosuppression (chemotherapy, cancer patients, HIV, those on corticosteroids, and organ transplant patients), those on indwelling catheter, parenteral nutrition and the illicit IV drug users [4],[7],[19],[25],[26],[27],[28].

To diagnose fPJI the surgeon should have a high suspension index, especially in high-risk patients. It is not routine to do all diagnostic tests, except in the most uncertain cases. We recommend following the WAIOT 10 golden rules of sampling for diagnosis of PJI, (Fig. 3) [29] and using the WAIOT definition of high and low grade PJI, Table 1 [30].

Figure 3: Microbiology best practice for the diagnosis of peri-prosthetic joint infections and implant-related infections in ortho-trauma. The 10 WAIOT golden rules. Reprinted with permission of Publisher. Open access reference [29]

	No Infection	Contamination	BIM	LG-PJI	HG-PJI
Clinical presentation	One or more condition(s), other than infection, can cause the symptoms or the reason for reoperation (e.g., wear debris, metallosis, recurrent dislocation or joint instability, fracture, malposition, neuropathic pain)		One or more of the followings: otherwise "unexplained" pain, swelling, stiffness		Two or more of the followings: pain, swelling, redness, warmth, *functio laesa*
# of Positive Rule IN minus # of Negative Rule OUT tests	<0	<0	<0	≥0	≥1
Post-operatively confirmed if	Negative cultural examination	One pre- or intra-operative positive culture, with negative histology	Positive cultural examination (preferably with antibiofilm techniques) and/or positive histology		

Abbreviations: WAIOT: World Association against Infection in Orthopedics and Trauma; BIM: Biofilm-related Implant malfunction; LG-PJI: Low-Grade Peri-Prosthetic Joint Infection; HG-PJI: High-Grade Peri-Prosthetic Joint Infection.

Table 1: WAIOT proposed definition of peri-prosthetic joint infection (PJI)

If fPJI is suspected, as it should be in elderly, revision, or re-revision, and those at risk, a plain x ray is ordered along with leukocyte count, blood culture and serum inflammatory markers (ESR, CRP and D-dimer). The leukocyte count is often normal [5],[31],[32]. The ESR, CRP and D-dimer may be normal or slightly elevated [4], [22],[33],[34]. Reports are inconsistent, with CRP values between 4 and 31 mg/dl [5],[31],[32] and ESR values of normal or at the low range, below 60mm/h [5],[9],[31].

A diagnostic arthrocentesis is performed, unless there is a sinus tract or exposed metal, and surgical debridement is a must [7],[13],[35]. Aspirate is analysed for low sugar, high protein, and cell count (more than 3000), although they may be of limited value [19]. The aspirate is sent for both bacterial and fungal cultures, the latter will take up to 4 weeks or longer [19]. Intraoperative samples are taken in accordance with WAIOT 10 rules and sent for cultures and histopathology [29].

Fungi are notoriously difficult to isolate [19], and although Candida is readily recovered using blood culture bottles (BCB) [36], but Sabouraud dextrose brain heart infusion (BHI) or plain BHI are universal media for most fungi, and other special media are required for other types of fungi [37],[38].

More sophisticated serology and molecular tests are not readily available, and their clinical use is still under investigation and include organism-specific antigens, serum beta-glucan, enzyme immunoassays, DNA based tests and mass spectrometry [20],[39]. In some culture -negative cases, uncultivable organisms should be considered, and other identification techniques are performed, such as polymerase chain reaction (PCR) and next generation sequencing (NGS) [4],[40].

Radiological assessment and diagnoses are beyond the scope of this review, but in fPJI all what may be needed is a plain x-ray. Although radionucleotide scans, MRI and CT are used in other fungal infections, their use in diagnosing and managing PJI is questionable [7],[41],[42],[43].

DISCUSSION

The literature lacks both evidence and clear algorithm regarding the best treatment approach in treating fPJI, but there has been preference toward certain surgical approaches and recommendations regarding both medical and surgical managements [4],[5],[7],[19],[44].

Regarding medical treatment, the Infectious Disease Society of America (IDSA) guidelines for the duration of treatment with antifungal agents in the treatment of joint arthritis are 6 to 12 months [12]. For Candida PJI, the European Society for Clinical Microbiology and Infectious Disease recommends implant removal with at least 14 days of parenteral antifungals followed by a subsequent minimum of 4 to 6 weeks of oral agents [4],[45],[46]. In the case of two-stage exchange, the International Consensus Meeting (ICM) recommends a minimum of 6 weeks antifungal treatment after prosthesis removal [4],[47]. A meta-analysis by Ueng et al. [8] identified an improved eradication of infection with prolonged systemic therapy from 3-6 months.

There is no agreement on the optimal choice of antifungal medication or whether to use monotherapy or combined therapy and the choice should be driven by resistance patterns and patient factors as well as the chronicity of the case. Most reports favor fluconazole, variconazole and amphotericin B [4],[5],[7]. The liposomal compounds of amphotericin B have a better record in reducing nephrotoxicity [7],[48],[49]. There are no existing guidelines for the use of prophylactic anti-fungal therapy in high-risk, immunocompromised patients going for total joint replacement [7].

There has not been adequate studies of the elution characteristics of antifungal agents from bone cement (PMMA) or calcium sulphates, although the commonly used amphotericin B was reported to have the longest elution properties of up to 100 days, but other agents including fluconazole and variconazole have been used also [7],[50]. A few papers have reported both In-vitro and In-vivo result to know more of the elution properties of antifungal agents as well as finding the best vehicle to assure a higher concentrations and longer elution. Butcher MC et al. [51] has reported on antifungal-loaded triple agents (fluconazole (FLZ), amphotericin B (AMB), and caspofungin

(CSP), calcium sulfate beads, producing a sustained antimicrobial effect that inhibits and kills clinically relevant fungal species in vitro as planktonic and biofilm cells. Romera D et al. [52] have reported a Novel hybrid organo-inorganic sol-gel coating of fluconazole or anidulafungin, with the highest concentration to prevent and locally treat yeast PJI. They have showed an excellent anti-biofilm behavior. Coatings loaded with fluconazole proved to be effective against both Candida species. The use of resorbable beads have been reported by Yung-Heng Hsu et al. [53]. They reported a high level of fluconazole (beyond the minimum therapeutic concentration [MTC]) release for more than 49 days, using biodegradable compression-molded PLGA (Poly(d,l-lactide-co-glycolide) /fluconazole beads.

Following surgical debridement, reports have had different approaches in dealing with fungal PJI. The numbers reported are small to draw firm conclusions, although recent meta-analysis and systematic reviews have shed more light into the best surgical approach in dealing with fPJI. The options at hand are DAIR (Debridement, Antibiotics, Implant Retention), one stage revision arthroplasty (Single-SRA), two stage revision arthroplasty (Two-SRA), three stage revision arthroplasty (Three-SRA), resection arthroplasty, arthrodesis, and amputation [4],[5],[7],[19],[21],[24],[54].

It has to be noted that amputation, arthrodesis, and resection arthroplasty (RA) may highly diminish the quality of life of the patients and the reported success rate of RA and arthrodesis from small series and heterogeneous reports is 80% and 67% respectively [7],[27], and that of amputation is 66% only [55]. Therefore, they should be sought of as a salvage procedure in the most resistance cases or those with repeated uncontrollable infection despite multiple procedures and long anti-fungal treatment. The reported surgical treatment methods come from small case series, case reports and systematic reviews and are heterogeneous [4],[5],[7],[12],[19],[26],[27],[44],[56].

Debridement, antibiotic, and implant retention (DAIR) have been used in small number of cases and mainly in cases reported within 4 weeks of the primary procedure and often resulting in persistent infection and 20-30% success rate only [4],[5],[24],[31]. For bacterial PJI, the consensus is that chronic infections should never be treated with DAIR, and the same has been suggested for fPJI, unless revision surgery is contraindicated or refused by the patient after adequate information [13],[24],[63].

In a recent systematic review, Sambri et al. [4] and Koutserimpas et al. [7] reported a predominance favoring of Two-SRA, (64.2%) and (54%) respectively. Other authors also reported a preference of Two-SRA among surgeons [9],[11],[19],[24],[26],[27],[55]. A success rate of over 92% has been reported for Two-SRA [7],[57],[58], although there is wide variability of success rate. Anagnostakos et al. [58] reported a 100% success in a small series of 7 patients. Haleem et al reported infection eradication up to above 90% [4],[57]. Kuiper et al [24] reported an 84.8% success rate, and Phelan et al [59] reported 80%. On the other hand, Azzam et al. [9] reported a 47.4% success rate only. It is notable that the success rate diminishes in the case of bacterial co-infection [7].

The optimal time interval for reimplantation is unknown. A minimum of six weeks is usually recommended [19], [24], although this is extended to 3-6 months in revision and re-revision cases [7]. In all cases reimplantation is performed when the clinical picture and blood markers have come to normal [24]. There is no conclusive evidence to support the use of an antimicrobial holiday period prior to reimplantation in case of fungal PJI treated with staged revision [21].

The Single-SRA has been used and reported with discordant results. A success rate of 90% has been reported by Klatte et al (60) in a small series of 10 patients. On the other hand, Ji et al [61] reported a recurrence rate of 36%. Others have reported a 75% success rate [7]. A Single-SRA might be considered in patients with unfit medical situation or those who may not tolerate multiple procedures, along with prolonged anti-fungal therapy.

The gold standard of bacterial PJI has been the Two-SRA, although Gregor Dersch and Heinz Winkler [62] have reported favorable and encouraging results of Single-SRA by using Antibiotic-Impregnated Cancellous Allograft Bone, on 70 cases. Whether their technique could be adopted for fPJI is for future research to decide.

Recently, a three-SRA for fungal PJI was reported and claimed 88.8% success [54]. This technique is in accordance with the recommendations of PRO-IMPLANT Foundation for difficult to treat (DDT) microorganisms [64]. The principles of this algorithm include, but are not limited to, the following key points:

First stage; debridement, removal of implant (sonication & culture). A custom-made cement spacer loaded with 0.4 g liposomal amphotericin B and voriconazole 0.4 g combined with 1 g gentamicin and 2 vancomycin per 40 g cement powder is used. If fungi not diagnosed preoperatively 1 g Gentamycine and 2 g Vancomycine spacer is used only.

Second stage; 3 weeks revision, debridement, and exchange of spacer. The same custom-made cement spacer with amphotericin B and voriconazole is used again to ensure continuously high local antimycotic therapy. The residual AB therapy will be adapted according to sonication.

Third stage; 3 weeks reimplantation. Again, debridement and final implantation of revision implant with custom made cement including amphotericin B 0.2 g and Voriconazol 0.2 g combined with 0.5 g Gentamicin and 2 g vancomycin is performed. This is followed by six months systemic anti-fungal treatment which is switched to oral after uneventful postoperative period and wound healing.

While Two-SRA appears as the most adopted surgical approach, there are no comparative studies, showing its superiority over Single-SRA, while the overall results of a 3-stage revision surgery do not seem to provide a substantial benefit, compared to 2-stage. In this regard, it should be noted that staged procedures are inevitably associated with additional operative risks, prolonged duration of the treatment and higher costs and an increase of the number of several subsequent procedures should be well balanced in each patient, weighing the potential benefits and risks.

RECOMMENDATIONS AND CONCLUSION

According to the presented data and review of literature, we believe that we can recommend the following generally agreed approach in treating fungal PJI, even if the specific treatment for each patient must be decided by the surgical team after open discussion with the patient and based on the general and local conditions, the clinical history and the expectations of the patient:

We believe that fPJI management lacks proper evidence and high volume, multi-center studies to draw sound conclusions regarding anti-fungal therapy agents, duration, combination treatment and success, as well as the best surgical options. In addition, more studies on the elution of antifungal agents, the minimum time interval between the two stages as well as establishing potent antibiofilm, antimicrobial agents and the possibility of using antifungal medications impregnation in bone graft in Single-SRA. These questions cannot be answered without the collaboration between multiple centers worldwide.

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