fungal PJIs often have an immunocompromised condition, such as diabetes mellitus, rheumatoid arthritis and cancer, which may markedly contribute to the high failure rate of treatments [3]. In addition, the complexity of the fungal biofilm in having a highly heterogeneous structure in response to environmental conditions, such as differences in pH, oxygen availability and redox potential, could also contribute to the suboptimal outcomes of treatment [4].

Overall, DAIR has been reported to have a relatively high failure rate in patients with PJIs caused by resistant organisms and poor hosts. DAIR as a surgical option for patients with fungal PJIs is questionable [5], and a study published in the *New England Journal of Medicine* listed fungal PJIs as a contraindication for DAIR [6]. A search of Medline, PubMed, Embase, Web of Science and Medscape revealed no reports in the setting of DAIR for acute fungal PJIs. The review of the English literature from 1979 to 2018 identified 22 fungal PJIs undergoing DAIR [7–19]. An overall high failure rate (82%, 18 of 22) was reported for these patients. Additionally, one study by Azzam et al. demonstrated a 100% failure rate for seven patients in their cohort undergoing DAIR [16]. Among the seven patients who failed, five needed resection arthroplasty and two needed chronic suppression with oral fluconazole [16]. Furthermore, Badrul et al. reported a fungal PJI case treated with debridement and oral fluconazole for a year. But, the infection was never totally cured and a secondary infection with methicillin-resistant *Staphylococcus aureus* (MRSA) developed [14]. Fabry et al. also reported a failure in a patient who underwent two debridements and an eight-month oral antifungal therapy regimen [15]. However, a few case reports demonstrated successful results at a minimum follow-up of two years and all of them required a six-months to one-year antifungal agent treatment after irrigation and debridement alone [9,11,12,18,19].

Given the fact that literature is not definitive on this issue and based on the available reports, we recommend that DAIR for fungal PJIs should be limited to those with early presentation, good soft tissue coverage, well-fixed implants and are healthy patients (Host type A). If DAIR is performed for patients with fungal PJIs, long-term suppression (six months or longer) with antifungal agents should also be considered.

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QUESTION 4: Which antifungals, route of administration and duration of treatment should be utilized to treat fungal periprosthetic joint infections (PJIs)?

RECOMMENDATION: Fluconazole, by both oral and intravenous routes, is currently the treatment of choice for PJIs due to susceptible fungi, including the *Candida* species which are responsible for the majority of fungal PJI cases. Amphotericin B lipid formulations or echinocandins given intravenously are secondary considerations, but may be less well tolerated. Culture data including antifungal susceptibilities should be used to guide therapy. Two-stage revision is currently the standard of care. Antifungal treatment should be administered during the spacer interval with a minimum treatment duration of six weeks. Following revision, treatment with oral fluconazole (400mg daily) should be continued for three to six months, if tolerated.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Fungal PJIs are uncommon, accounting for approximately 1% of PJIs [1,2]. *Candida* species, in particular *Candida albicans*, are by far the most common pathogen [1,3]. Concomitant bacterial infection may occur in up to 20% of cases [4]. Risk factors for fungal

PJIs include immunosuppression, systemic disease and extended antimicrobial therapy [5]. *Candida* infections are associated with biofilm formation which plays a key role in the development of PJIs [5,6]. Given the infrequency of fungal PJIs, there are no standard guidelines regarding treatment. The current literature contains retrospective case series and case reports. There are no randomized clinical trials, prospective cohort studies or case-control studies to guide therapeutic decisions.

Candida PJI has been treated successfully with antifungal therapy alone in several case reports [7,8]. Two-stage revision, however, is regarded to be the current standard of care for the surgical management of fungal PJI as high failure rates have been reported with primary debridement. Debridement, antibiotics and implant retention (DAIR), as well as single-stage revision, were shown to have a failure rate of up to 50% [1,2,9,10]. A two-stage revision with interval antibiotic therapy is consistent with the Infectious Diseases Society of America (IDSA) guidelines for bacterial PJI [11]. The role of antifungal eluting bone cement is controversial. Fluconazole is not currently available as a sterile powder. Both amphotericin B and voriconazole can be added to cement. Data show that voriconazole is more effectively released than amphotericin B and that it achieves and maintains high intra-articular concentrations [12–17].

Systemic antifungal therapy is administered during the spacer interval. Treatment options include fluconazole (400mg (6mg/kg) PO/IV daily), an echinocandin (caspofungin 50 to 70mg IV daily, micafungin 100mg IV daily or anidulafungin 100mg IV daily) or lipid formulation amphotericin B (3-5 mg/kg IV daily) [18]. The minimum duration of antifungal therapy after resection should be 6 weeks with up to 12 weeks considered. Revision surgery should be delayed three to six months in most cases [18,19]. Antifungal therapy should be discontinued and aspiration of the joint space should be culture-negative prior to revision. Following revision, fluconazole (200mg to 400mg PO daily) should be continued for a minimum of six weeks with up to six months or longer considered [2,5,18,20].

The incidence of fungal PJI is expected to rise given the increasing number of joint arthroplasties performed each year [21]. While specific guidelines for the management of fungal PJI have yet to be established, important considerations in management include confirmation of microbiologic diagnosis including antifungal susceptibility testing of fungal isolates, surgical options with two-stage exchange arthroplasty currently favored, the use of antifungal eluting cement and long-term systemic antifungal therapy.

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