

G84: What is the optimal antimicrobial treatment for patients with orthopedic infections caused by Fungi?

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Response/Recommendation:

Culture data, including antifungal susceptibility testing, should guide therapy. Fluconazole is currently the treatment of choice for fungal orthopedic infections, including *Candida* species. Echinocandins or Amphotericin B lipid formulations given intravenously are alternative options, though they may be less well tolerated by patients. Voriconazole is the preferred treatment for *Aspergillus* spp. orthopedic infections.

Level of Evidence: Moderate

Delegate Vote:

Rationale:

Fungal orthopedic infections are uncommon, accounting for approximately 1.3% of periprosthetic joint infections (PJIs), with *Candida* PJIs specifically accounting for >90% of all fungal PJIs [1]. *Candida* species, in particular *Candida albicans*, are by far the most common pathogen. Combined infection with bacterial species may occur in up to 51.3% of cases [1]. Guan's study demonstrated that the treatment success rate was 47.4% (9/19) in fungal PJI cases with bacterial co-infection, significantly lower than those without [vs. 79.0% (45/57), $P=0.017$] [2]. A binary logistic regression model showed that bacterial co-infection and surgical option were the two significant risk factors associated with treatment failure for fungal PJI following hip arthroplasty [2].

Risk factors for fungal PJIs include immunosuppression, systemic disease, repeated surgery, previous *Candida* infection and extended antimicrobial therapy [1, 3]. *Candida* infections are associated with biofilm formation, which plays a key role in the development of orthopedic infections. Given the infrequency of orthopedic infections caused by fungi, there are no standard guidelines regarding treatment. The IDSA guidelines address candidiasis more generally, with some emphasis on orthopedic infections requiring surgical intervention [4]. The current literature contains retrospective cohort studies, case series, case reports and one prospective cohort study. There are no randomized clinical trials, or case-control studies to guide therapeutic decisions.

Two-stage or one stage revision arthroplasty is regarded to be the current standard of care for the surgical management of fungal PJIs. Debridement, antibiotics, and implant retention (DAIR) with the absence of prosthesis exchange was a major factor associated with failure [1]. The pooled success rate for surgical debridement, spacer implantation, resection arthroplasty, one-stage revision, and two-stage revision was 50.0% (4/8), 42.9% (3/7), 55.0% (11/20), 86.7% (13/15), and 88.5% (23/26), respectively, with significant differences between them ($p=0.009$) [2].

Systemic antifungal therapy is administered during the spacer interval between stages of surgery. Treatment options include fluconazole 400 mg (6 mg/kg) PO/IV daily, an echinocandin (caspofungin 50-70 mg IV daily, micafungin 100 mg IV daily or anidulafungin 100 mg IV daily) or lipid formulation amphotericin B (3-5 mg/kg IV daily) [4]. Better antibiofilm

activity has been demonstrated in vitro, but the clinical effect remains under debate. The minimum duration of antifungal therapy after resection should be 6 weeks with up to 12 weeks considered in more severe cases; following revision surgery, fluconazole 400 mg IV for 14 days, followed by oral fluconazole (400 mg daily) should be continued for a minimum of 6 weeks, with the total duration extending up to 12 months or longer, depending on patient response and culture susceptibilities [4, 5, 6]. Voriconazole is a treatment of choice for *Aspergillus* spp. orthopedic infections [7].

With the absence of published literature, there is no evidence to support antibiotic holidays before second stage. Emerging evidence shows that antibiotic holiday may in fact increase the rate of failure of two stage exchange and its role in management of patients with chronic PJI undergoing two stage exchange needs to be reexamined (Ascione et al, Fraval et al)

Three-stage revision arthroplasty with prolonged systemic antifungal therapy [8], adding of antibiotics, including rifampicin (even in the absence of bacterial growth) [9, 10], antibiofilm antifungal treatment as initial treatment [8, 3], Amphotericin B added to cement [8, 9] showed promising results in some studies but require further investigation to confirm efficacy and safety.

Conclusion:

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

References:

1. Dinh A, McNally M, D'Anglejan E, Mamona Kilu C, Lourtet J, Ho R, Scarborough M, Dudareva M, Jesuthasan G, Ronde Oustau C, Klein S, Escolà-Vergé L, Rodriguez Pardo D, Delobel P, Lora-Tamayo J, Mancheño-Losa M, Sorlí Redó ML, Barbero Allende JM, Arvieux C, Vaznaïsiène D, Bauer T, Roux AL, Noussair L, Corvec S, Fernández-Sampedro M, Rossi N, Lemaïnen A, Costa Salles MJ, Cunha Ribeiro T, Mazet J, Sasso M, Lavigne JP, Sotto A, Canouï E, Senneville É, Thill P, Lortholary O, Lanternier F, Morata L, Soriano A, Giordano G, Fourcade C, Franck BJH, Hofstätter JG, Duran C, Bonnet E; European Society of Clinical Microbiology and Infectious Diseases Study Group on Implant Associated Infections (ESGIAI). Prosthetic Joint Infections due to *Candida* Species: A Multicenter International Study. Clin Infect Dis. 2024 Aug 27;ciae395. doi: 10.1093/cid/ciae395. Epub ahead of print. Erratum in: Clin Infect Dis. 2024 Nov 22;79(5):1324. doi: 10.1093/cid/ciae492. PMID: 39189831.
2. Guan Y, Zheng H, Zeng Z, Tu Y. Surgical procedures for the treatment of fungal periprosthetic infection following hip arthroplasty: a systematic scoping review. Ann Med Surg (Lond). 2024 Mar 4;86(5):2786-2793. doi: 10.1097/MS9.0000000000001864. PMID: 38694320; PMCID: PMC11060286.

3. Escolà-Vergé L, Rodríguez-Pardo D, Lora-Tamayo J, Morata L, Murillo O, Vilchez H, Sorli L, Carrión LG, Barbero JM, Palomino-Nicás J, Bahamonde A, Jover-Sáenz A, Benito N, Escudero R, Sampedro MF, Vidal RP, Gómez L, Corona PS, Almirante B, Ariza J, Pigrau C; 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. *J Infect*. 2018 Aug;77(2):151-157. doi: 10.1016/j.jinf.2018.03.012. Epub 2018 May 8. PMID: 29746950.
4. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016 Feb 15;62(4):e1-50. doi: 10.1093/cid/civ933. Epub 2015 Dec 16. PMID: 26679628; PMCID: PMC4725385.
5. Miller AO, Gamaletsou MN, Henry MW, Al-Hafez L, Hussain K, Sipsas NV, Kontoyiannis DP, Roilides E, Brause BD, Walsh TJ. Successful treatment of *Candida* osteoarticular infections with limited duration of antifungal therapy and orthopedic surgical intervention. *Infect Dis (Lond)*. 2015 Mar;47(3):144-9. doi: 10.3109/00365548.2014.974207. Epub 2014 Dec 24. PMID: 25539148.
6. Ueng SW, Lee CY, Hu CC, Hsieh PH, Chang Y. What is the success of treatment of hip and knee candidal periprosthetic joint infection? *Clin Orthop Relat Res*. 2013 Sep;471(9):3002-9. doi: 10.1007/s11999-013-3007-6. Epub 2013 Apr 30. PMID: 23633184; PMCID: PMC3734391.
7. Kumashi PR, Safdar A, Chamilos G, Chemaly RF, Raad II, Kontoyiannis DP. Fungal osteoarticular infections in patients treated at a comprehensive cancer centre: a 10-year retrospective review. *Clin Microbiol Infect*. 2006 Jul;12(7):621-6. doi: 10.1111/j.1469-0691.2006.01471.x. PMID: 16774557.
8. Baecker H, Frieler S, Geßmann J, Pauly S, Schildhauer TA, Hanusrichter Y. Three-stage revision arthroplasty for the treatment of fungal periprosthetic joint infection: outcome analysis of a novel treatment algorithm : a prospective study. *Bone Jt Open*. 2021 Aug;2(8):671-678. doi: 10.1302/2633-1462.28.BJO-2021-0002.R2. PMID: 34406077; PMCID: PMC8384437.
9. Wang QJ, Shen H, Zhang XL, Jiang Y, Wang Q, Chen YS, Shao JJ. Staged reimplantation for the treatment of fungal peri-prosthetic joint infection following primary total knee arthroplasty. *Orthop Traumatol Surg Res*. 2015 Apr;101(2):151-6. doi: 10.1016/j.otsr.2014.11.014. Epub 2015 Feb 9. PMID: 25676891.
10. Grzelecki D, Grajek A, Dudek P, Olewnik Ł, Zielinska N, Fulin P, Czubak-Wrzosek M, Tyrakowski M, Marczak D, Kowalczewski J. Periprosthetic Joint Infections Caused by *Candida* Species-A Single-Center Experience and Systematic Review of the Literature. *J Fungi (Basel)*. 2022 Jul 29;8(8):797. doi: 10.3390/jof8080797. PMID: 36012786; PMCID: PMC9410158.