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QUESTION 2: Should patients with periprosthetic joint infections (PJIs) caused by a fungus undergo the typical two-week antimicrobial holiday prior to reimplantation?

RECOMMENDATION: 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.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The review of the literature on fungal PJIs treated with staged revision shows only 8 retrospective cohort studies (level of evidence IV) and 13 case reports (level of evidence V) (Table 1). We have been able to find only 21 papers (104 patients) regarding fungal PJI treated with two-stage exchange arthroplasty. In 68 cases (from 14 different studies), a drug holiday of at least two weeks was applied before reimplantation. No drug holiday was prescribed in two cases. For the remaining 34 patients, there was no data available about this aspect. Candida spp. (especially *albicans* or *parapsilosis*) was the main causal agent. Most patients had at least six weeks of systemic antifungal treatment after first operation, in agreement with the 2013 Consensus Conference conclusions. Following reimplantation, antifungal agents were continued for from two weeks to six months in six studies (69 patients). The agent most frequently used was fluconazole. Among reviewed papers, most authors seem to prefer a drug holiday of two or more weeks before second surgical stage. This approach is consistent with the conclusion of the previous Consensus Conference in 2013. No study compares the results of the two different strategies.

In conclusion, antifungal therapy could be stopped before reimplantation but there is no high-quality evidence to support this opinion.

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TABLE 1. Retrospective cohort studies regarding the recommendation duration of systemic antifungal agents for fungal periprosthetic joint infection treated with two-stage exchange arthroplasty

Author	Year	N	Organism	Length of Anti-fungal Therapy	Length of Interstage	Drug Holiday	Outcome
Hennessy [1]	1996	1	*C. parapsilosis*	13 w	not known	not known	cured
Ramamohan [2]	2000	1	*C. glabrata*	6 w	6 w	0	cured
Yang [3]	2001	1	*C. parapsilosis*	10 w	3 m	2 w	cured
Baumann [4]	2001	1	*A. fumigatus*	6 w	8 w	2 w	cured
Phelan [5]	2002	10	Candida spp.	25 w (2-49)	6.7 m (8 days-17.7 m)	1.4 m	8 cured
Cutrona [6]	2002	1	*R. minuta*	not known	12m	not known	cured
Wyman [7]	2002	1	*C. tropicalis*	not known	not known	not known	cured
Azzam [8]	2009	31 (19 with two-stage)	*C. albicans* (20) *C. parapsilosis* (4) both above (3) *C. glabrata* (1) Aspergillus (1) Others (2)	6 w after RA 6 m after reimplantation	7 m (range 2-14)	≥2 w	9 cured/ 10 failed
Dutronc [9]	2010	7 (3 with two-stage)	*C. albicans* (4) *C. parapsilosis* (2) *C. guilliermondii* (1)	not known	not known	not known	1 cured/ 2 failed
Wu and Hsu [10]	2011	1	*C. albicans*	17 w after RA 6 m after reimplantation	6 m	7 w	cure
Yilmaz	2011	1	*A. fumigatus*	6 w	4 m	10 w	cure
Graw [11]	2010	2	*C. albicans*	12 w	not known	8 w- 1 y	failed
Hwang [12]	2012	28	*C. parapsilosis/albicans*	≥6 w after RA A maximum of 6 m after reimplantation	9.5 w (6-24)	not known	22 cured/ 4 failed
Anagnastakos [13]	2012	5	*C. albicans (2)* *C. lypolitica* *C. albicans+C. glabrata* *C. glabrata*	6 w	12.8 w (12-14)	6.8 w (6-8)	cured
Kuiper [14]	2013	8 (4 with two-stage)	*C. albicans* (6) *C. albicans* + *C. glabrata* *C. parapsilosis* (1)	8.75 w (1w-5mo)	6.5 m (4-14 m)	>8 w (8-50w)	2 cured/ 2 failed
Deelstra [15]	2013	1	*C.albicans*	not known	not known	no	cured
Ueng [16]	2013	8	Candida spp	14 m after RA (3-18 m) 2.5 m after reimplantaiton	not known	≥2 w	8 cured/ 1 deceased

Author	Year	N	Organism	Length of Anti-fungal Therapy	Length of Interstage	Drug Holiday	Outcome
Reddy [17]	2013	1	*C. tropicalis*	18	20 w	2 w	cured
Wang [18]	2015	5	Candida spp	8 w after RA (6-10) 2 w after reimplantation	6 m	>2 m	5 cured
Geng [19]	2016	8	*C. albicans* (3) Mould *C. freyschussii* Aspergillus spp *C. parapsilosis* *C. glabrata*	2.8 m after RA (1.5-6) 1m after reimplantation (1m-46 days)	4.3 m (3-7)	6 w (2w-10w)	7 cured
Sebastian [20]	2017	1	*C. tropicalis*	24 w	9 m	3 m	cure

RA, resection arthroplasty

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QUESTION 3: Can debridement, antibiotics and implant retention (DAIR) be used to treat acute fungal periprosthetic joint infections (PJIs)?

RECOMMENDATION: DAIR has a relatively high failure rate in fungal PJIs, especially for immunocompromised patients. DAIR should be reserved for patients with truly acute PJIs after an index arthroplasty and in healthy patients (Type A). If DAIR is performed for fungal PJIs, consideration should be given to anti-fungal suppression therapy.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 5%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

PJIs caused by fungal pathogens are a rare occurrence accounting for <1% of all PJIs [1]. Surgical treatments for fungal PJIs include DAIR, one-stage exchange arthroplasty and two-stage exchange arthroplasty. The difficultly in the treatment of fungal PJIs can be attributed to the rarity of fungal PJIs that have confined our understanding of this infectious entity and the often-immunocompromised status of patients who develop these infections in the first place. Although some general agreements have been reached with recommendations proposed by the International Consensus Meeting (ICM) and Infectious Diseases Society of America (IDSA) [2,3], many issues related to fungal PJIs remain unresolved. The most optimal surgical option for patients with fungal PJIs, the dose and the type of antifungals to be added to the polymethyl methacrylate (PMMA) spacer, the optimal duration of systemic antifungal treatment and many other issues still remain unanswered.

In addition, despite offering a potential explanation above, the exact reason for the less optimal outcomes of treatment of fungal PJIs remains unknown. It is, however, known that patients with