SYSTEMATIC REVIEWS

Non-*albicans Candida* prosthetic joint infections: A systematic review of treatment

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Abstract

BACKGROUND
Non-*albicans Candida* prosthetic joint infections (PJIs) are rare. Optimal treatment involves a two-stage revision surgery in combination with an antifungal agent. However, no clear guidelines have been developed regarding the agent or treatment duration. Hence, a broad range of antifungal and surgical treatments have been reported so far.

AIM
To clarify treatment of non-*albicans Candida* PJIs.

METHODS
A literature review of all existing non-*albicans Candida* PJIs cases through April 2018 was conducted. Information was extracted about demographics, comorbidities, responsible species, duration and type of antifungal treatment, type of surgical treatment, time between initial arthroplasty and symptom onset, time between symptom onset and definite diagnosis, outcome of the infection and follow-up.

RESULTS
A total of 83 cases, with a mean age of 66.3 years, were located. The causative

yeast isolated in most cases was *C. parapsilosis* (45 cases; 54.2%), followed by *C. glabrata* (18 cases; 21.7%). The mean Charlson comorbidity index was 4.4 ± 1.5. The mean time from arthropalsty to symptom onset was 27.2 ± 43 mo, while the mean time from symptom onset to culture-confirmed diagnosis was 7.5 ± 12.5 mo. A two stage revision arthroplasty (TSRA), when compared to one stage revision arthroplasty, had a higher success rate (96% *vs* 73%, *P* = 0.023). Fluconazole was the preferred antifungal agent (59; 71%), followed by amphotericin B (41; 49.4%).

CONCLUSION
The combination of TSRA and administration of prolonged antifungal therapy after initial resection arthroplasty is suggested on the basis of limited data.

Key words: Fungal prosthetic joint infection; Knee arthroplasty infection; Hip arthroplasty infection; Antifungal treatment; Non-*albicans Candida* prosthetic joint infections

Core tip: Non-*albicans Candida* prosthetic joint infections (PJIs) are rare, and no clear guidelines exist regarding the treatment of these infections. The purpose of this study was to clarify, by reviewing current published cases, the treatment options of non-*albicans Candida* PJIs and, possibly, to improve the medical and surgical care of such cases. A literature review of all existing non-*albicans Candida* PJIs cases through April 2018 was conducted. The combination of two stage revision arthroplasty and administration of prolonged antifungal therapy after initial resection arthroplasty is suggested on the basis of limited data.

INTRODUCTION

Prosthetic joint infection (PJI) is a severe complication of joint surgery, involving the joint prostheses and contiguous tissue, representing a main cause of total arthroplasty failure[1]. A plethora of microorganisms have been held responsible for these infections, such as Gram-positive and negative bacteria, while fungal microorganisms are considered rare causes. Fungal PJIs occur in about 1-2% of all cases, while the most common spread type seems to be hematogenous[2].

Optimal treatment is considered the two stage revision surgery in combination with an antifungal agent. However, no clear guidelines have yet been developed regarding the agent and treatment duration. Hence, a broad range of antifungal and surgical treatments have been reported so far[3,4].

Candida spp represent the most common fungal pathogens for PJIs, with *Candida albicans* being the most prevalent species. However, over the last years, the incidence of non-*albicans Candida* PJIs has increased[4,5]. The purpose of this study was to clarify, by reviewing current published cases, the treatment options of non-*albicans Candida* PJIs in order to potentially improve the medical and surgical care of such cases.

MATERIALS AND METHODS

A search of PubMed and MEDLINE databases was performed to identify all existing articles reporting the management of non-*albicans Candida* PJIs cases through April 2018. Isolated and combined terms of "fungal prosthetic joint infection", "fungal arthroplasty infection", "fungal hip arthroplasty infection", "fungal knee arthroplasty infection", "fungal shoulder arthroplasty infection", as well as terms including each non-*albicans Candida* species (*e.g.*, "*candida glabrata* joint infection", "*candida parapsilosis* joint infection, *etc*) were used. The citations in each article were reviewed to locate

additional references that were not retrieved during the initial search.

The present review is limited to papers published in English, peer-reviewed journals. Furthermore, cases without information about management and treatment were excluded. The data extracted from these studies included age, gender, affected joint, responsible non-*albicans Candida* species, duration and type of antifungal treatment, type of surgical treatment, time between initial arthroplasty and symptom onset, time between symptom onset and definite diagnosis (culture), outcome of the infection and follow-up of each case. Charlson Comorbidity score was calculated, when possible, by two independent investigators based on the information provided from each report.

Data were recorded and analyzed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington). Two-sided Fisher's exact tests were used to compare success rates between groups. Statistical analyses were carried out at the 5% level of significance.

RESULTS

Table 1 highlights the findings from the electronic search, covering a 39 year period ending in 2018. A total of 83 non-*albicans Candida* PJIs were identified[4,6-47]. A total of 46 cases (55.4%) were female patients, thirty-six male (43.4%), while in one case the gender was not clarified. The mean age of the study population was 66.3 years [standard deviation (SD) = 10.2]. The affected joint was the knee in 52 cases (62.6%), the hip in 29 (35%) and the shoulder in two (2.4%). Two of the knee prosthetic joint cases were bilateral. The mean Charlson comorbidity index of patients was 4.4 (SD = 1.5).

The mean time from initial arthroplasty implantation surgery to symptom onset was 27.2 mo (SD = 43), while the mean time from symptom onset to culture-confirmed diagnosis was 7.5 mo (SD = 12.5). Regarding the causative non-*albicans Candida* species, the most frequently isolated one was *C. parapsilosis*, found in 45 cases (54.2%), followed by *C. glabrata* in 18 (21.7%), *C. tropicalis* in ten (12%), *C pelliculosa* in three (3.6%) and *C. lusitanae* in two (2.4%), while *C. famata*, *C. lipolytica*, *C. utilis*, *C. guilliermondii* and *C. freyschussii* had caused one case each (1.2%) (Figure 1).

Regarding surgical treatment, in the majority of the described cases (44 cases; 53%) a two stage revision arthroplasty (TSRA) was performed, followed by resection arthroplasty (RA) (18 cases; 22%), one stage revision arthroplasty (OSRA) (eight cases; 9.6%), arthrodesis (five cases; 6%), debridement (three cases; 3.6%) and amputation (two cases; 2.4%). In three cases (3.6%), there was no surgical treatment (Figure 2). TSRA exhibited a success rate of 96%, RA a rate of ≥ 61% [in 7 cases information about the infection outcome was not provided (studies 8, 31, 32, 46, 60, 62, 66 in Table 1)], OSRA a rate of 73%, debridement a rate of 75%, amputation a rate of 100%, while no surgical treatment has shown a success rate of 60%. TSRA when compared to OSRA had a higher success rate (96% *vs* 73%; *P*-value = 0.023).

Regarding the preferred antifungal agent, 38 cases (45.8%) were treated with a single drug, 29 (34.9%) with two, 12 (14.5%) with more than two, while one case did not receive antifungal treatment [(1.2%); case 17 in Table 1; the antifungal agent was not reported in case 32].

Fluconazole was used in most cases [59; (71%), in 31 of them (52.5%) as monotherapy], followed by amphotericin B [41; (49.4%), in 4 (9.8%) as monotherapy], flucytosine [13; (15.7%), in 1 (7.7%) as monotherapy], caspofungin [7; (8.4%), in 1 (14.3%) as monotherapy], voriconazole [7; (8.4%), in 2 (28.6%) as monotherapy], ketoconazole [5; (6%), none as monotherapy], itraconazole [3; (3.6%), none as monotherapy] and anidulafungin [l; (1.2%), not as monotherapy]. The final outcome was successful in 74 cases (89.2%).

The majority of patients with *C. parapsilosis* PJIs were treated with fluconazole [30 cases; (66.7%), in 22 (73.3%) as monotherapy], followed by amphotericin B [19; (42.2%), none as monotherapy], flucytosine [8; (17.8%), in 1 (12.5%) as monotherapy], ketoconazole [3; (6.7%), none as monotherapy], while voriconazole and itraconazole were used in 1 case each (none as monotherapy). Outcome was successful in 40 cases (88.9%).

The majority of cases with *C. glabrata* PJIs were treated with amphotericin B [8; (44.4%), in 1 (12.5%) as monotherapy], followed by fluconazole [7; (38.9%), in 3 (42.9%) as monotherapy]. Caspofungin and voriconazole were used in 5 cases (27.8%) each, in 1 (20%) case each as monotherapy. Furthermore, three (16.7%) patients received flucytosine (none as monotherapy), two (11.1%) itraconazole (none as monotherapy) and one (5.6%) anidulafungin (not as monotherapy). Outcome was successful in 17 cases (94.4%), while one patient (case number 11 in Table 1) passed

Table 1 Non-*albicans Candida* prosthetic joint infection cases

Ref.	Year	Fungus	Gender	Age	Joint	Charlson comorbidity index	Antifungal treatment	Surgical treatment	Treatment duration	Outcome	Follow-up in mo	Time from implantation to symptoms onset in mo	Time from symptoms onset to definite diagnosis by culture, in mo
Koutserimpas *et al*[6]	2018	*C. glabrata*	Female	68	Knee	4	Anidulafungin / Voriconazole	TSRA	28 wk	Successful	-	180	0.5
Geng *et al*[7]	2016	*C. glabrata*	Male	78	Hip	4	Fluconazole / Amphotericin B / Caspofungin	Spacer implantation (failure)/ RA	26 wk	Successful		11	34.8
Klatte *et al*[8]	2014	*C. glabrata*	Female	81	Hip	4	Flucytosine / Amphotericin. B / Fluconazole	OSRA	-	Successful		8	-
Zhu *et al*[9]	2014	*C. glabrata*	Male	44	Hip	-	Amphotericin B / Voriconazole	No	6 wk	Successful	3	-	5
Anagnostakos *et al*[10]	2012	*C. glabrata*	Female	51	Hip	6	Fluconazole	TSRA	6 wk	Successful	70	-	-
Anagnostakos *et al*[10]	2012	*C. glabrata*	Male	78	Hip	6	Fluconazole	TSRA	6 wk	Successful	15	-	-
Bartalesi *et al*[11]	2012	*C. glabrata*	Female	60	Hip	-	Voriconazole / Caspofungin + Amphotericin B	TSRA	6 wk	Successful	48	-	-
Hall *et al*[12]	2012	*C. glabrata*	Female	60	Hip	4	Caspofungin	RA	6 wk	-	-	< 0.5	0.2
Dumaine *et al*[13]	2008	*C. glabrata*	-	72	Knee	5	Caspofungin + Flucytosine / Fluconazole + Flucytosine	Arthrodesis	16 wk	Successful	15	-	-
Lejko-Zupanc *et al*[14]	2005	*C. glabrata*	Male	74	Hip	5	Amphotericin B + Fluconazole / Caspofungin	RA	→ 3 wk	Successful	36	72	-
Fabry *et al*[15]	2005	*C. glabrata*	Female	74	Knee	6	Voriconazole	2x Debridement	32 wk	Death from unrelated causes while on therapy	24	72	-
Gaston *et al*[16]	2004	*C. glabrata*	Female	42	Knee	4	Voriconazole / Amphotericin B	Amputation (above knee)	8 wk	Successful	6	264	-

Author	Year	Organism	Sex	Age	Joint		Antifungal	Procedure	Duration	Outcome			
Açikgöz et al[17]	2002	C. glabrata	Female	70	Knee	-	Fluconazole	Arthrodesis	-	Successful	7.5	9	6
Ramamo-han et al[18]	2001	C. glabrata	Female	65	Hip	-	Amphotericin B + Flucytosine	TSRA	7 wk	Successful	24	48	-
Selmon et al[19]	1998	C. glabrata	Female	75	Knee	5	Amphotericin B/Itraconazole + Fluconazole	OSRA	> 8 wk	Successful	48	84	-
Nayeri et al[20]	1997	C. glabrata	Female	62	Hip	4	Amphotericin B+ Flucytosine / Itraconazole + Flucytosine	OSRA	11 wk	Successful	22	60	-
Darouiche et al[21]	1989	C. glabrata	Female	69	Hip	-	Amphotericin B	RA	1 wk	Successful	-	27	0.5
Goodman et al[22]	1983	C. glabrata	Female	69	Hip	3	-	RA	-	Successful	12	27	-
Geng et al[7]	2016	C. papapsilosis	Male	67	Knee	3	Fluconazole	TSRA	10 wk	Successful	48	3	-
Wang et al[23]	2015	C. parapsilosis	Female	67	Knee	4	Fluconazole	TSRA	10 wk	Successful	27	-	-
Wang et al[23]	2015	C. parapsilosis	Male	74	Knee	5	Fluconazole	TSRA	8 wk	Successful	30	-	-
Wang et al[23]	2015	C. pasapsilosis	Female	71	Knee	4	Fluconazole	TSRA	6 wk	Successful	62	-	-
Klatte et al[8]	2014	C. parapsilosis	Male	69	Knee	8	Flucytosine+ Amphotericin. B	OSRAx3 (Failure the first 2 times)	-	Successful	19	1	-
Klatte et al[8]	2014	C. parapsilosis	Female	82	Knee	4	Flucytosine+ Amphotericin. B	OSRA	-	Successful		2	-
Klatte et al[8]	2014	C. parapsilosis	Male	46	Knee	1	Flucytosine+ Amphotericin. B	OSRA	-	Successful		6	-
Ueng et al[24]	2013	C. parapsilosis	Male	62	Knee	4	Fluconazole	TSRA	-	Successful	≥ 24	4.5	1.5
Ueng et al[24]	2013	C. parapsilosis	Male	77	Knee	-	Fluconazole	TSRA	-	Successful	≥ 24	4	3
Ueng et al[24]	2013	C. parapsilosis	Male	66	Hip	-	Fluconazole	TSRA	-	Successful	≥ 24	2	1
Ueng et al[24]	2013	C. parapsilosis	Male	76	Knee	8	Fluconazole	TSRA	-	Successful	≥ 24	33	2
Ueng et al[24]	2013	C. parapsilosis	Male	36	Knee	-	Fluconazole	TSRA	-	Successful	≥ 24	74	2
Ueng et al[24]	2013	C. parapsilosis	Male	66	Hip	4	Fluconazole	RA	-	-	-	2	2
Kuiper et al[25]	2013	C. parapsilosis	Male	58	Hip	-	None	RA/refused further treatment	-	Refused further treatment	8	-	-
Chiu et al[26]	2013	C. parapsilosis	Male	71	Hip	5	Fluconazole	RA	40 wk	Successful	24	48	-
Hwang et al[4]	2012	C. parapsilosis	Female	71	Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	46	-	-

Hwang et al[4]	2012	C. parapsilosis	Female	76	Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	56	-	-
Hwang et al[4]	2012	C. parapsilosis	Female	76	Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	67	-	-
Hwang et al[4]	2012	C. parapsilosis	Female	72	Knee	-	Fluconazole	TSRA	≥ 6 wk	Successful	73	-	-
Hwang et al[4]	2012	C. parapsilosis	Female[1]	61[1]	Bilateral Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	65	-	-
Hwang et al[4]	2012	C. parapsilosis	Female[1]	61[1]	Bilateral Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	46	-	-
Hwang et al[4]	2012	C. parapsilosis	Female	67	Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	65	-	-
Hwang et al[4]	2012	C. parapsilosis	Female	68	Knee	-	Fluconazole,	TSRA	≥ 6 wk	Successful	69	-	-
Hwang et al[4]	2012	C. parapsilosis	Female	68	Knee	-	Fluconazole,	TSRA	≥ 6 wk	Successful	42	-	-
Hwang et al[4]	2012	C. parapsilosis	Female	67	Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	49	-	-
Hwang et al[4]	2012	C. parapsilosis	Female	60	Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	41	-	-
Hwang et al[4]	2012	C. parapsilosis	Female	73	Knee	-	Amphotericin B / Fluconazole	TSRA	≥ 6 wk	Successful	52	-	-
Anagnostakos et al[10]	2012	C. parapsilosis	Male	67	Knee	-	Fluconazole	RA	6 wk	-	-	-	-
Dutronc et al[27]	2010	C. parapsilosis	Male	66	Hip	5	Fluconazole	TSRA	24 wk	Successful	-	0	-
Dutronc et al[27]	2010	C. parapsilosis	Female	77	Hip	4	Ampotericin B + fluorocytosine / Fluconazole	RA	38 wk	Successful	-	5	-
Antony et al[28]	2008	C. parapsilosis	Female	67	Shoulder	3	Voriconazole / Fluconazole	TSRA	-	Successful	6	-	-
Antony et al[28]	2008	C. parapsilosis	Female	67	Hip	3	Fluconazole	TSRA	-	Successful	-	-	-
Yang et al[29]	2001	C. parapsilosis	Female	68	Knee	3	Fluconazole	TSRA	10 wk	Successful	48	0	16
Bruce et al[30]	2001	C. parapsilosis	Female	51	Hip	-	Fluconazole	TSRA	-	Successful	84	36	36
Brooks[31]	1998	C. parapsilosis	Male	64	Knee	5	Amphotericin B/Fluconazole	Debridement	28 wk	Successful	24	15	4
Wada et al[32]	1998	C. parapsilosis	Male	77	Knee	4	Fluconazole	Debridement	28 wk	Successful	36	0.5	0.5
Cushing et al[33]	1997	C. parapsilosis	Female	73	Knee	-	Fluconazole	No	> 24 wk	Successful	12	1	-
Fukasawa et al[34]	1997	C. parapsilosis	Female	80	Knee	-	Fluconazole	Debridement	53 wk	Successful	24		2

White *et al*[35]	1995	*C. parapsilosis*	Female	64	Knee	-	Fluconazole/Amphotericin B/Itraconazole	RA	20 wk	Successful	-	0	9
Tunkel *et al*[36]	1993	*C. parapsilosis*	Male	37	Knee	6	Amphotericin B/Ketoconazole/Fluconazole	TSRA (Failure)/Amputation (Successful)	-	Successful	7	4	0
Paul *et al*[37]	1992	*C. pasapsilosis*	Male	63	Knee	-	Amphotericin + fluorocytosine/ketoconazole	Arthrodesis	9 wk	Successful	24	3	4
Lim *et al*[38]	1986	*C. parapsilosis*	Male	35	Knee	-	Fluorocytosine	Arthrodesis	-	-	-	0	6
Younkin *et al*[39]	1984	*C. parapsilosis*	Female	75	Hip	-	Fluorocytosine+Amphotericin B	TSRA	6 wk	Successful	24	0	60
Lichtman[40]	1983	*C. parapsilosis*	Male	59	Shoulder	-	Amphotericin B/ketoconazole	RA	Indefinite (> 58 d)	-	-	20	9
MacGregor *et al*[41]	1979	*C. parapsilosis*	Male	64	Knee	-	Amphotericin B + Fluorocytosine	Non-surgical (failure)/then RA	21 wk	Successful	12	27	5
Sebastian *et al*[42]	2017	*C. tropicalis*	Male	53	Hip	3	Fluconazole	TSRA	28 wk	Successful	NR	24	0
Reddy *et al*[43]	2013	*C. tropicalis*	Female	62	Knee	3	Fluconazole	TSRA	30 wk	Successful	24	22.5	1.5
Ueng *et al*[24]	2013	*C. tropicalis*	Male	67	Hip	-	Fluconazole	RA	-	-	-	15	1
Lidder *et al*[44]	2013	*C. tropicalis*	Female	76	Hip	-	Amphotericin B	RA	24 wk	Successful	24	36	15
Azam *et al*[45]	2008	*C. tropicalis*	Male	73	Hip	6	Caspofungin/Fluconazole	TSRA	≥ 9 wk, (Caspofungin 1 wk, fluconazole ≥ 8 wk)	Successful	12	108	-
Wyman *et al*[46]	2002	*C. tropicalis*	Male	62	Knee		Fluconazole/Amphotericin B	TSRA	18 wk	Successful	36	0.25	6
Darouiche *et al*[21]	1989	*C. tropicalis*	Male	72	Hip	4	Amphotericin B/ketoconazole	Debridement (failure)/RA	12 wk	Successful	36	0.5	1
Lambertus *et al*[47]	1988	*C. tropicalis*	Male	61	Hip	3	Amphotericin B	RA	-	Successful	24	6	6
Lambertus *et al*[47]	1988	*C. tropicalis*	Male	65	Hip	-	Amphotericin B/ketoconazole	RA/arthrodesis	>24 wk	Successful	14	4	4
73.Goodman *et al*[30]	1983	*C. tropicalis*	Female	59	Knee	-	Amphotericin B	TSRA (failure)/RA	6 wk	Successful	12	3	6
Hwang *et al*[4]	2012	*C. pelliculosa*	Female	67	Knee	-	Fluconazole	TSRA	≥ 6 wk	Successful	56	-	-
Hwang *et al*[4]	2012	*C. pelliculosa*	Female	64	Knee	-	Amphotericin B/fluconazole	TSRA	≥ 6 wk	Successful	35	-	-

Hwang *et al*[4]	2012	*C. pelliculosa*	Male	75	Knee	-	Amphotericin B / fluconazole	TSRA	≥ 6 wk	Successful	34	-	-
Klatte *et al*[8]	2014	*C. lusitaniae*	Male	74	Knee	6	Voriconazole	OSRA	-	Successful		12	-
Hwang *et al*[4]	2012	*C. lusitaniae*	Female	66	Knee	-	Amphotericin B / fluconazole	TSRA	≥ 6 wk	Successful	43	-	-
Hwang *et al*[4]	2012	*C. famata*	Female	83	Knee	-	Amphotericin B / fluconazole	TSRA	≥ 6 wk	Successful	33	-	-
Anagno-stakos *et al*[10]	2012	*C. lipolytica*	Male	77	Hip	7	Fluconazole	TSRA	6 wk	Successful	22	-	-
Wang *et al*[23]	2015	*C. utilis*	Female	56	Knee	2	Fluconazole	TSRA	6 wk	Successful	24	-	5
Dutronc *et al*[27]	2010	*C. guiller-mondii*	Male	76	Knee	4	Amphotericin B+ fluorocytosine / Fluconazole	None	14 wk (2 wk AMB+ 5FC, then 3 mo FZ)	Failure	-	0	-
Geng *et al*[7]	2016	*C. frey-schussii*	Female	58	Knee	2	Fluconazole / Caspofungin	TSRA	10 wk	Successful	55	<0.25	

Patient demographics, antifungal treatment, its duration, as well as infection outcome and follow-up period are presented.
[1]Bilateral PJI in the same patient; -: Not reported or unclear. TSRA: Two stage revision arthroplasty; OSRA: One stage revision arthroplasty; RA: Resection arthroplasty.

away from unrelated causes.

The majority of *C. tropicalis* PJIs were treated with amphotericin B [6; (60%), in 3 (50%) as monotherapy], followed by fluconazole [5; (50%), in 3 (60%) as monotherapy], ketoconazole [2; (20%), none as monotherapy] and caspofungin [1; (10%), not as monotherapy]. Outcome was successful in 9 cases (90%; case number 66 in Table 1, treated with fluconazole as monotherapy, did not provide information about outcome).

All patients suffering from *C. pelliculosa* PJI received fluconazole [3 cases; (100%), 1 (33.3%) as monotherapy], while 2 of them (66.7%) received amphotericin B (none as monotherapy). All patients (100%) were treated successfully. Both patients suffering from *C.lusitaniae* were treated successfully. Voriconazole was used as monotherapy in 1 case (50%), while amphotericin B and fluconazole were used in the other.

One patient suffering from *C. famata* was successfully treated with amphotericin B and fluconazole, while fluconazole as monotherapy was successfully used for the treatment of each case of *C. lipolytica* and *C. utilis* PJI. One case of *C. freyschussii* was successfully treated with fluconazole and caspofungin. A case of *C. guilliermondii* infection received amphotericin B, fluorocytosine and fluconazole, however, the result was failure. The mean antifungal treatment duration was 12.8 wk (SD = 10.9), while the mean follow-up of these cases was 33.3 mo (SD = 19.6).

DISCUSSION

Fungal invasive infections, such as PJIs, due to *Candida* species have been acknowledged as a major cause of morbidity and mortality. These infections have been associated with progress in medical modalities, and is some cases have been considered iatrogenic[3,4]. *Candida* PJIs are relative rare, since only case reports or small case series have been reported so far. *Candida albicans* is the most prevalent species. However, the incidence of invasive candidiasis and PJIs due to non-*albicans Candida* is increasing[5,48]. Optimal treatment of these infections remains unclear, since no certain guidelines exist for the antifungal, as well as for the surgical treatments[48]. It is, therefore, of paramount importance to report such cases and to obtain a better understanding of treatment options and outcomes of these infections. The present study is an effort to review, in a systematic way, the non-*albicans Candida* PJI cases
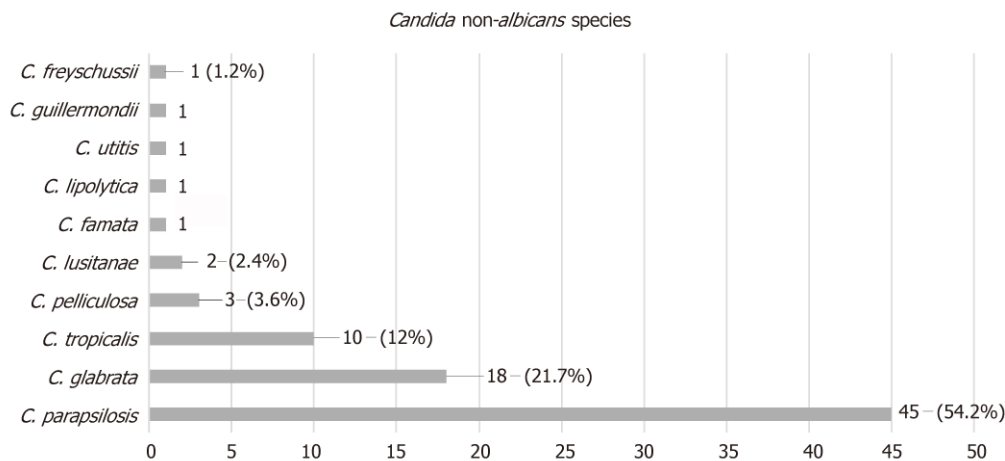
Figure 1 Prosthetic joint infection causative non-*albicans Candida* species.

DISCUSSION

Fungal invasive infections, such as PJIs, due to *Candida* species have been acknowledged as a major cause of morbidity and mortality. These infections have been associated with progress in medical modalities, and is some cases have been considered iatrogenic[3,4]. *Candida* PJIs are relative rare, since only case reports or small case series have been reported so far. *Candida albicans* is the most prevalent species. However, the incidence of invasive candidiasis and PJIs due to non-*albicans Candida* is increasing[5,48]. Optimal treatment of these infections remains unclear, since no certain guidelines exist for the antifungal, as well as for the surgical treatments[48]. It is, therefore, of paramount importance to report such cases and to obtain a better understanding of treatment options and outcomes of these infections. The present study is an effort to review, in a systematic way, the non-*albicans Candida* PJI cases described in the literature. The study focuses on the preferred antifungal agent, the optimal surgical treatment, and the duration of therapy.

The electronic search has revealed a total of 83 patients with non-*albicans Candida* PJI. Their mean age was 66.3 years. Although *Candida* PJI is still considered rare, its incidence is expected to rise, due to the increasing number of joint arthroplasty surgeries performed worldwide[2,48].

Several risk factors have been identified for invasive candidiasis, such as immunosuppression, long-term antimicrobial use and systemic disease[3,4,5,48]. Such a patient profile has been illustrated by the relatively high mean Charlson comorbidity index of the present study's population, found to be 4.4.

Candida PJI is most commonly considered of hematogenous origin[2,6,48]. The mean time between initial arthroplasty surgery and symptomatology onset in the study population was 27.2 mo, while it ranged from immediately after surgery to 264 mo. It is of note that in 13 cases [15.7%; cases 8, 23, 47, 51, 54, 55, 57, 60, 61, 69, 70, 82, 83 (Table 1)] this time was found to be less than 1 mo. Therefore, in these cases the spread should be considered perioperative.

It is also of interest that the mean time between symptomatology onset and definite (culture-based) diagnosis was 7.5 mo, ranging from immediately after onset to 60 mo. This could be attributed to the fact that the main symptoms of *Candida* PJI are non-specific, which mainly include pain and swelling[1-5,48]. The symptomatology onset may be mild, insidious and slowly progressive. Therefore, diagnosis may be delayed due to low suspicion index.

The most frequently isolated non-*albicans Candida* spp was *C. parapsilosis*, found in 45 cases (54.2%), followed by *C. glabrata* in 18 (21.7%), *C. tropicalis* in 10 (12%), *C pelliculosa* in 3 (3.6%), *C. lusitanae* in 2 (2.4%) and 1 case each (1.2%) of PJI caused by *C. famata*, *C. lipolytica*, *C. utitis*, *C. guillermondii* and *C. freyschussii*.

In the present study, *C. parapsilosis* was found to be the predominant pathogen causing PJIs, as compared to other non-*albicans Candida* species. *C. parapsilosis* prevalence has dramatically increased over the last 3 decades. Infections due to this pathogen are more frequently associated with prosthetic devices, indwelling catheters and hyperalimentation solutions. The pathogenesis of the infection depends on the expression of virulence factors, including adherence to host cells and tissues, biofilm formation and secretion of extracellular hydrolytic enzymes[5,49].

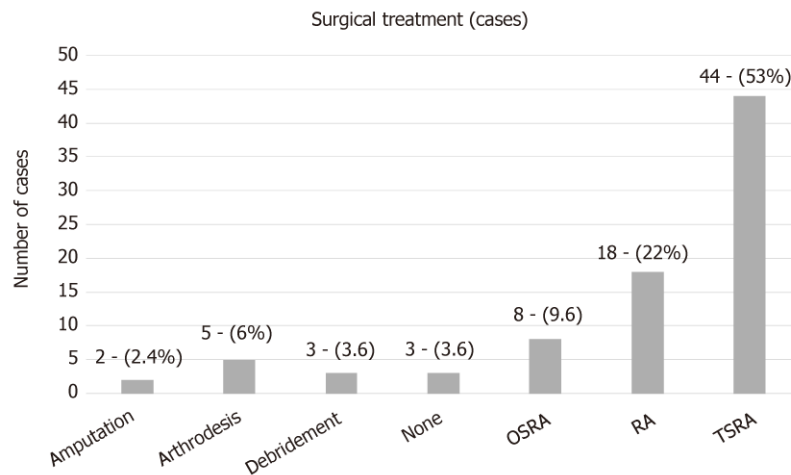The treatment of *C. parapsilosis* PJIs has proven to be successful in 88.9% of the

Figure 2 Surgical treatment for non-*albicans Candida* prosthetic joint infection. TSRA: Two stage revision arthroplasty; OSRA: One stage revision arthroplasty; RA: Resection arthroplasty.

studied cases. This is probably due to the fact that echinocandines were not used for the treatment of such cases, taking into account that *C. parapsilosis'* MICs are usually elevated to echinocandins, as compared to other *Candida* spp[50].

Treatment of *C. glabrata* PJIs has been successful in 94.4% of the studied cases. This is probably due to the fact that an azole compound has rarely been used for treatment and, in the limited number of cases when an azole was used, the drug has been given in combination with another antifungal, taking into account that *C. glabrata* is often resistant to azoles[50]. In most cases of *C. tropicalis* PJIs, treatment has been successful, since either single antifungal agents or combinations are known to be effective against this *Candida* spp.

All cases of *C. pelliculosa* PJIs have been treated successfully due to the use of effective agents. *C. lusitaniae* is intrinsically resistant to amphotericin B[50,51]. One case received this agent in combination with fluconazole, while the other one was treated with voriconazole as monotherapy. Hence, finally, the 2 cases caused by *C. lusitanae* were successfully treated.

The cases of *C. famata*, *C. lypolitica* and *C. utilis* were successfully treated with the antifungals given. It is of note that the single case of *C. guillermondii*, although treated with a combination of antifungals, resulted in failure. For successful treatment, it is of the utmost importance to carry out susceptibility testing to obtain accurate MIC values following *Candida* isolation, taking into account that different *Candida* species are characterized by intrinsic resistance to certain antifungal compounds. Regarding the preferred antifungal agent, fluconazole was used in most cases [59; (71%), in 31 of them (52.5%) as monotherapy], followed by amphotericin B [41; (49.4%), in 4 (9.8%) as monotherapy]. Fluconazole has been rarely associated with severe hepatotoxicity. Therefore, liver function tests should be performed regularly during prolonged fluconazole therapy[50,51]. Amphotericin B is an effective broad spectrum agent. However, it is relatively toxic and its side effects, including renal dysfunction, may restrict its long-term use, which is essential in PJI cases[6]. Echinocandines are the most recently developed anti-Candida agents. Although C. parapsilosis strains mostly exhibit high MICs, these agents can often be clinically effective due to their immunomodulatory properties and the fact that they successfully penetrate biofilms[52].

The mean duration of antifungal treatment in the study population was 12.8 wk, while it ranged from 1 to 53 wk. One case (case 32 in Table 1) did not receive any antifungal treatment. Guidelines for the treatment of osteoarticular infections from *Candida* spp exist. However, no clear recommendations are available for the treatment of such PJIs[6,48]. Therefore, the treatment duration is mainly based on the clinical and laboratory findings of each case.

Several options for surgical treatment have also been described. In the study population, in most cases (44 cases; 53%) a TSRA was performed, followed by RA (18 cases; 22%), OSRA (8 cases; 9.6%), arthrodesis (5 cases; 6%), debridement (3 cases; 3.6%) and amputation (2 cases; 2.4%).Three cases did not receive surgical treatment (3.6%; case 4, 55 and 82 in Table 1). RA, arthrodesis, amputation and debridement are usually considered alternative options to arthroplasty exchange. TSRA had a statistically significant higher success rate when compared to OSRA (96% *vs* 73%; *P*-

value = 0.023). Therefore, it seems more proper that TSRA should be considered as the optimal surgical intervention.

The present review has shown that non-*albicans Candida* PJIs represent a dangerous reality. Optimal management consists of a combination of the proper medical antifungal treatment based on susceptibility testing and surgical intervention. Although there have been reports of successful treatment of such cases with OSRA and debridement only, TSRA should be strongly recommended. The combination of TSRA separated by 3–6 mo and a prolonged period of antifungal therapy is suggested on the basis of limited data. Additional issues, such as the duration of antifungal therapy after prosthesis implantation (second stage of the TSRA), as well as the role of antifungal-loaded cement spacers, need to be addressed in order to determine the optimal treatment combinations.

ARTICLE HIGHLIGHTS

Research background
Prosthetic joint infection (PJI) represents a severe complication of joint reconstruction surgery, causing total arthroplasty failure. Many pathogens have been identified in PJIs, such as Gram-positive and negative bacteria, while fungal microorganisms are considered rare causes, occurring in 1-2% of cases. *Candida* spp represent the most common fungal pathogens in these infections, with *Candida albicans* being the most prevalent species. However, the incidence of non-*albicans Candida* PJIs has increased over the last years. Hence, regarding non-*albicans Candida* PJIs, only case reports or small series have been reported so far. Optimal treatment is considered the two stage revision surgery in combination with an antifungal agent. However, no clear guidelines have yet been developed regarding the agent and treatment duration. Hence, a broad range of antifungal and surgical treatments has been reported so far. The present review article represents the first effort of evaluating the reported non-*albicans Candida* PJIs, aiming to clarify the treatment options of these infections and, possibly, to improve the medical and surgical care of such cases.

Research motivation
The absence of clear guidelines regarding fungal PJIs represents a primary issue in managing these infections in clinical practice. A broad range of antifungal and surgical treatments have been reported, while treatment duration remains unclear. Furthermore, due to the limited data regarding these infections, information about patient demographics, responsible non-*albicans Candida* species, time between initial arthroplasty and symptom onset, time between symptom onset and definite diagnosis (culture), and outcome of the infection has not been reported in a systematic way. Hence, it is of utmost importance in the future to report such cases in order to obtain a better understanding about this devastating arthroplasty complication.

Research objectives
The main objective of this study was to clarify, by systematically reviewing current published cases in the literature, the treatment options of non-*albicans Candida* PJIs and, possibly, to improve the medical and surgical care of such cases. During the process of reviewing the literature, it became apparent that information about patient demographics, fungal species, time between initial arthroplasty and symptom onset, time between symptom onset and definite diagnosis (culture), as well as outcome of the infection should also be reported, due to the absence of a systematic review regarding this topic.

Research methods
A meticulous electronic search of PubMed and MEDLINE databases was performed to identify all articles reporting the management of non-*albicans Candida* PJIs cases through April 2018 by two independent investigators. The citations in each article were reviewed to locate additional references that were not retrieved during the initial search. The evaluated parameters were patient demographics and comorbidities, affected joints, responsible non-*albicans Candida* species, duration and type of antifungal treatment, type of surgical treatment, time between initial arthroplasty and symptom onset, time between symptom onset and definite diagnosis (culture), and outcome of the infection. Data were recorded and analyzed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, Washington). Two-sided Fisher's exact tests were used to compare success rates between groups. Statistical analyses were carried out at the 5% level of significance.

Research results
A total of 83 non-*albicans Candida* PJIs were located, with a mean age of 66.3 years (SD = 10.2). The knee was the affected joint in 52 cases (62.6%), the hip in 29 (35%) and the shoulder in 2 (2.4%). The mean time from arthroplasty to symptoms onset was found to be 27.2 mo (SD = 43), while the mean time from symptoms onset to culture-confirmed diagnosis was 7.5 mo (SD = 12.5). The most commonly isolated non-*albicans Candida* species was *C. parapsilosis*, found in 45 cases (54.2%), followed by *C. glabrata* in 18 (21.7%), *C. tropicalis* in 10 (12%), *C pelliculosa* in 3 (3.6%) and *C. lusitanae* in 2 (2.4%), while *C. famata*, *C. lipolytica*, *C. utilis*, *C. guilliermondii* and *C. freyschussii* had caused one case each (1.2%). A two stage revision arthroplasty (TSRA) was performed in most cases (44 cases; 53%), followed by RA (18 cases; 22%), OSRA (8 cases; 9.6%),

arthrodesis (5 cases; 6%), debridement (3 cases; 3.6%) and amputation (2 cases; 2.4%), while 3 cases (3.6%) received no surgical treatment. TSRA when compared to OSRA had a higher success rate (96% *vs* 73%; *P*-value = 0.023). Fluconazole was used in most cases as antifungal treatment [59; (71%), in 31 of them (52.5%) as monotherapy], followed by amphotericin B [41; (49.4%), in 4 (9.8%) as monotherapy], flucytosine [13; (15.7%), in 1 (7.7%) as monotherapy], caspofungin [7; (8.4%), in 1 (14.3%) as monotherapy], voriconazole [7; (8.4%), in 2 (28.6%) as monotherapy], ketoconazole [5; (6%), none as monotherapy], itraconazole [3; (3.6%), none as monotherapy] and anidulafungin [l; (1.2%), none as monotherapy]. The final outcome was successful in 74 cases (89.2%). The mean antifungal treatment duration was 12.8 wk (SD = 10.9), while the mean follow-up of these cases was 33.3 mo (SD = 19.6). The present review has shown that the optimal management of non-*albicans Candida* consists of a combination of the proper medical antifungal treatment and surgical intervention. Although there have been reports of the successful treatment of such cases with OSRA and debridement only, TSRA should be strongly recommended. The combination of TSRA and a prolonged period of antifungal therapy based on susceptibility testing is suggested on the basis of limited data. Additional issues, such as the duration of antifungal therapy after prosthesis implantation (second stage of the TSRA) and the role of antifungal-loaded cement spacers need to be addressed in order to determine an optimal treatment combination.

Research conclusions

The present study is an effort to review, in a systematic way, the non-*albicans Candida* PJI cases described in the literature. The study focuses on the preferred antifungal agent, the optimal surgical treatment, and the duration of therapy. *C. parapsilosis* was found to be the predominant pathogen causing PJIs, as compared to other non-*albicans Candida* species. For successful management of non-*albicans Candida* PJI, susceptibility testing to obtain accurate MIC values should always be performed following the *Candida* isolation, considering that different *Candida* species are characterized by intrinsic resistance to certain antifungal compounds. The mean duration of antifungal treatment in the present review was 12.8 wk, while it ranged from 1 to 53 wk. Although, guidelines for the treatment of osteoarticular infections from *Candida* spp are available, no clear recommendations exist for the treatment of such PJIs. Therefore, the treatment duration is mostly based upon clinical and laboratory findings. In most cases (44 cases; 53%) a TSRA was performed, followed by RA (18 cases; 22%), OSRA (8 cases; 9.6%), arthrodesis (5 cases; 6%), debridement (3 cases; 3.6%) and amputation (2 cases; 2.4%). Three cases did not receive surgical treatment (3.6%). RA, arthrodesis, amputation and debridement are usually considered alternative options to arthroplasty exchange. TSRA when compared to OSRA had a statistically significant higher success rate (96% *vs* 73%; *P*-value= 0.023). Therefore, it seems more proper that TSRA should be considered as the optimal surgical intervention. The present review has shown that the optimal management of non-*albicans Candida* PJIs consists of a combination of the proper medical antifungal treatment based on susceptibility testing and a surgical intervention, while TSRA should be strongly recommended. The combination of TSRA separated by 3–6 mo, in addition to a prolonged period of antifungal therapy, is suggested.

Research perspectives

Non-*albicans Candida* PJIs represent a dangerous reality. The combination of TSRA separated by 3–6 mo and a prolonged period of antifungal therapy is suggested on the basis of limited data. It is of paramount importance to report the treatment of such cases, even the failed ones, in order to obtain a better understanding of these infections and to determine the optimum treatment combination.

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