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Review Article

Selection of Antifungals in Bone Cements for the Treatment of Fungal Prosthetic Joint Infections - A Systematic Review

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Abstract

Background: Although antibiotic-impregnated bone cement has been widely used for the treatment of bacteria prosthetic joint infections, the use of antifungal-impregnated bone cement (AF-BC) in the treatment of Fungal Prosthetic Joint Infections (F-PJIs) remains unclear. This systematic review aims to summarise the use of AF-BC for the treatment of F-PJIs.

Methods: A literature search was performed using Ovid Medline, Embase, CINHAL and Cochrane via the Ovid platform from inception until August 2023. Screening was performed by two independent reviewers with a third for discrepancies.

Results: Out of 191 articles identified, 25 articles met the inclusion criteria describing 102 joints in which AF-BC was employed. All studies were case reports or case series, and no randomized controlled trials. Majority of the cases were caused by Candida species (95%). Amphotericin B was the preferred antifungal (86%) with a mean dose of 0.37g ± 0.25g per 40g bag of cement but ranged from 0.1-1.2g. Of the 81 cases that achieved infection free survival, the mean time for AF-BC was 25 weeks (range 3-60).

Conclusion: Our systematic review showed that a 2-stage reimplantation approach using AF-BCs combined with systemic antifungal therapy was successful in treating majority of F-PJIs. However, due to the small sample size, specific recommendations regarding the use of antifungal treatment in bone cements cannot be made. The combination of 0.3g of amphotericin B and 1.8g of vancomycin per 40g of bone cement demonstrated successful infection-free survival at the 12-month follow-up in most reported cases.

Introduction

Fungal prosthetic joint infections (F-PJIs) are rare, accounting for less than 1% of all PJIs [1]. With few reported cases and the lack of a specific treatment protocol, F-PJIs represent a therapeutic challenge [2]. F-PJIs pose greater challenges compared to bacteria PJIs for several reasons: 1) they are less common, leading to potential misdiagnosis and delayed treatment; 2) F-PJIs tend to be chronic and insidious, making eradication more difficult; 3) fungal organisms have complex cell walls and unique biochemical pathways, making them more resistant to antifungal agents than bacteria are to antibiotics. Some fungal species may also form biofilms, which are dense and protective communities that are difficult for antifungal agents to penetrate; and 4) Surgical management of F-PJIs is more complex, requiring extensive debridement and leading to increased morbidity and longer hospital stays.

In the absence of therapeutic guidelines for the management of F-PJI, most studies adopt the two-stage revision arthroplasty as the treatment of choice [2,3]. The largest F-PJI clinical study to date by Herndon et al reported a success rate of less than 50% with most cases associated with bacterial co-infection [4]. Systemic antifungals have limited effectiveness at the implantation site, leading to considerations of local antifungal treatments as effective adjuncts [5]. Antifungal-impregnated bone cements (AF-BCs) are preferred for local drug delivery. However, AF-BCs have some limitations including antifungal resistance development, hypersensitivity reactions, decreased mechanical strength of bone cements, increased surgical time and increased cost. Due to limited clinical data, the efficacy of AF-BCs remains controversial. This systematic review aims to consolidate available evidence on AF-BCs use in managing F-PJIs and try to identify optimal management regimes.

Material and Methods

Study Design

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [6].

Literature Search

The authors conducted a literature search to identify studies on the use of AF-BCs for the treatment of F-PJIs. Various databases including Ovid Medline, Embase, CINHAL and Cochrane via the Ovid platform were searched without date restrictions but limited to English language publications. Specific keywords and Medical Subject Headings (MeSH) were used in the search strategy that is supplied in Appendix 1. The initial search was performed on 22 July 2021 and an update was conducted on 14 August 2023. Additionally, related references and cited articles were manually searched to find any additional relevant studies for inclusion.

Inclusion and Exclusion Criteria

The inclusion criteria for the study were PJIs caused by fungal pathogens; and patients undergoing surgical revision with the use of AF-BCs irrespective of the pathogen type or surgical treatment strategy. Studies were excluded if they did not report outcomes for AF-BC use in F-PJIs, if necessary, data could not be extrapolated or calculated from published results, non-English texts, and studies falling into categories like reviews, animal studies, in-vitro studies, or mechanical studies.

Selection Process

After the literature search, duplicates were removed, and the remaining citations were screened for eligibility. Covidence, a web-based systematic review tool was employed to assist with citation importing and screening, full text review, study selection, data extraction and data exporting. WPJT and ATGM independently screened all titles and abstracts to identify eligible studies based on the predefined criteria. The studies were then reviewed in full text by both reviewers for final inclusion. Disagreements were resolved by consensus between the two reviewers and the senior author (PJS) was available to resolve any disagreements if consensus could not be met.

Data Items

The following information were collected: author, year of publication, demographic data (age, gender), site of infection, causative fungal pathogen, presence of bacteria/ fungal co-infection, cement type, details of antifungals with or without antibiotics impregnated in bone cements, surgical approach, type and length of systemic antifungals, complications and length of follow-up (Tables 2 &3).

Table 1: Antifungal impregnated into bone cements.

	Amphotericin B	Voriconazole	Fluconazole
Number of cases Δ	88	12	3
Gram of antifungal per 40g of bone cements	0.37 ± 0.25 (0.1 - 1.2)	0.48 ± 0.30 (0.1 – 1.0)	2

Δ two antifungal agents (amphotericin B and voriconazole) were used in one case.

Table 2: Overview of treated cases, demographic data and causative organism(s).

	Study ID	Year	#	Age	Sex	Joint	Fungal	Bacteria Co-infection
1	Kurmis (Kurmis, 2021)	2021	1	70	M	Knee	A. fumigatus	Group B Streptococcus
2	Mafrachi et al. (Mafrachi et al., 2021)		2	60	F	Knee	C. parapsilosis	-
3	Ornell et al. (Ornell et al., 2019) 2019	2021	3	57	F	Elbow	C. parapsilosis	CoNS, MSSA
4	Nowbakht et al. (Nowbakht et al., 2017)	2017	4	77	M	Knee	H. capsulatum	-
5	Skedros et al. (Skedros et al., 2014)	2014	5	58	M	Shoul-der	C. glabrata	Serratia marcescens

6	Frieler et al. (Frieler et al., 2020)	2020	6	58	F	Knee	C. parapsilosis	Enterococcus faecium
7	Gao et al. (Gao et al., 2018)	2018	7	78	F	Knee	C. tropicalis, C. parapsilosis	-
			8	63	F	Knee	C. albicans	-
			9	63	F	Knee	C. albicans	-
			10	52	F	Knee	A. strictum	-
			11	54	M	Knee	C. parapsilosis	Staphylococcus
			12	67	M	Knee	C. parapsilosis	-
			13	66	M	Knee	C. parapsilosis	Staph epidermidis, Pseudomonas aeruginosa
8	Kim et al. (Kim et al., 2018)	2018	14	89	F	Knee	C. parapsilosis	MRSE
			15	88	F	Knee	C. parapsilosis	-
			16	80	F	Knee	C. parapsilosis	-
			17	71	F	Knee	C. parapsilosis	-
			18	67	F	Knee	C. parapsilosis	-
			19	75	M	Knee	C. parapsilosis	-
			20	67	F	Knee	C. parapsilosis	-
			21	73	F	Knee	C. parapsilosis	-
			22	72	F	Knee	C. parapsilosis	MRSA
9	Burgo et al. (Burgo et al., 2018)	2018	23	73	F	Hip	T. inkin	Klebsiella pneumoniae
10	Geng et al. (Geng et al., 2016)	2016	24	67	M	Knee	C. parapsilosis	-
11	Wang et al. (Wang et al., 2015)	2015	25	67	F	Knee	C. parapsilosis	-
			26	56	F	Knee	C. utilis	-
			27	74	M	Knee	C. parapsilosis	-
			28	68	M	Knee	P. anomala	Staph auricularis
			29	71	F	Knee	C. parapsilosis	-
12	Wiwattanawarang (Wiwattanawarang, 2014)	2014	30	69	M	Knee	Candida spp.	-
13	Denes et al. (Denes et al., 2012)	2012	31	55	M	Hip	C. glabrata	-
			32	55	M	Hip	C. glabrata	-
14	Gaston and Ogden (Gaston and Ogden, 2004)	2004	33	42	F	Knee	C. glabrata	-
15	Bruce et al. (Bruce et al., 2001)	2001	34	51	F	Hip	C. parapsilosis	-
			35	68	F	Hip	C. albicans	-
16	Bottagisio et al. (Bottagisio et al., 2021)	2021	36	75	F	Hip	C. albicans	-
17	Wu and Hsu (Wu and Hsu, 2011)	2011	37	72	M	Knee	C. intertrigo, C. albicans	-
18	Reddy et al. (Reddy et al., 2013)	2013	38	62	F	Knee	C. tropicalis	-
19	Deelstra et al. (Deelstra et al., 2013)	2013	39	73	F	Hip	C. albicans	CoNS
20	David et al. (David M. et al., 2002)	2002	40	75	F	Hip	C. albicans	-

21	Baecker et al. (Baecker et al., 2021)	2021	41	85	10F 8M	Hip	C. famata	Staph epidermidis
			42	66		Knee	C. parapsilosis	-
			43	81		Hip	C. albicans	-
			44	67		Hip	C. famata	Citrobacter koseri
			45	81		Knee	C. tropicalis	Staph epidermidis
			46	81		Hip	C. parapsilosis	Staph caprae
			47	56		Knee	C. albicans	-
			48	78		Hip	C. parapsilosis	-
			49	66		Knee	C. glabrata	Escherichia coli
			50	81		Hip	C. famata	-
			51	57		Knee	C. parapsilosis	-
			52	82		Hip	C. albicans	-
			53	79		Knee	C. albicans	-
			54	78		Hip	C. albicans	Staph epidermidis
			55	60		Hip	C. parapsilosis	Strep sanguinis
			56	71		Knee	C. albicans	-
			57	83		Hip	A. infectoria	-
			58	57		Hip	C. albicans	-
22	Morimoto et al. (Morimoto et al., 2021)	2021	59	73	M	Hip	C. albicans	-
23	Oenning et al. (Oenning et al., 2020)	2020	60	55	F	Knee	C. albicans	-
24	Giordani et al. (Giordani et al., 2023)	2023	61	34	M	Knee	Coccidioidomycosis	-
25	Yang et al. (Yang et al., 2023)	2023	62-102	77.6 ± 7.6	31F 10M	Knee	C. parapsilosis (30)	MRSE (5)
							C. glabrata (7)	MRSA (3)
							C. albicans (2)	Other bacteria (5)
							C. rugosa (1)	
							C. pelliculosa (1)	

CoNS: coagulase negative staphylococcus; MSSA: methicillin sensitive staphylococcus aureu; MRSA: methicillin resistant staphylococcus aureus; MRSE: Methicillin resistant staphylococcuys epidermidis

Table 3: Surgical and Antifungal Treatment, Follow-up, and Infection Outcome of Reported Cases.

	Bacteria infection	2-stage interval / wks	Bone cement	Antifungal per 40g of bone cement	Antibiotic per 40g of bone cement	Systemic Antifungal Treatment (AFT)	Duration of AFT /mth	Follow-up /mth	Out-come	Com-plica-tions
1	Yes	15	Copal® G+V	Voriconazole 0.15g	Nil	Nil	Nil	12	IFS	Nil
2	No	12	n.s.	Amphotericin B	Nil	PO caspofungin 0.05 g/d + PO fluconazole 0.2g/d for 40 days followed by PO fluconazole 0.15 g/d for 6 wks	3	12	IFS	Nil
3	Yes	n.s.	n.s.	Amphotericin B	Vancomycin, Tobramycin	PO fluconazole	6	12	IFS	Nil
4	No	36	n.s.	Voriconazole 0.2g	Nil	PO itraconazole 0.4 g/d	9	24	IFS	Nil
5	Yes	12	n.s.	Amphotericin B	Nil	Nil	Nil	12	Failure	Nil
6	Yes	3	n.s.	Amphotericin B 0.4g	Gentamicin 0.5g, Vancomycin 4g	IV caspofungin for 10 days followed by PO fluconazole for 6 wks	2	36	IFS	Nil

7	No	12	Palacos® MV+G	Voriconazole 0.4g	Vancomycin 3g, Meropenem 1g	IV fluconazole	1.5	28	IFS	Leukopenia
8	No	64	Palacos® MV+G	Amphotericin B 0.3g	Vancomycin 0.6g	IV voriconazole for 6 wks followed by PO fluconazole for 12 wks	4.5	26	Failure	Nil
9	No	68	Palacos® MV+G	Voriconazole 1g	Vancomycin 1.3g	IV voriconazole for 4 wks followed by PO fluconazole for 8 wks	3	26	Failure	Nil
10	No	36	Palacos® MV+G	Voriconazole 0.13g	Vancomycin 1.3g, Meropenem 1g	IV voriconazole for 6 wks followed by PO fluconazole for 12 wks	4.5	30	IFS	Nil
11	Yes	16	Palacos® MV+G	Voriconazole 0.4g	Vancomycin 3g	IV fluconazole for 6wks	3	32	Failure	Abnormal sound
12	No	16	Palacos® MV+G	Amphotericin B 0.2g	Vancomycin 2g	PO fluconazole for 6 wks followed by IV fluconazole for 6 wks	1.5	66	IFS	Nil
13	Yes	52	Palacos® MV+G	Amphotericin B 1.25g	Vancomycin 5g	IV fluconazole for 6 wks followed by PO fluconazole for 6 wks	3	64	IFS	Nil
14	Yes	6	n.s.	Amphotericin B	Vancomycin, Cefazolin, Tobramycin	PO fluconazole 0.2-0.4 g/d	7 (4-15)	144	IFS	Nil
15	No	8	n.s.	Amphotericin B	Vancomycin, Tobramycin			90	IFS	Nil
16	No	6	n.s.	Amphotericin B	Vancomycin, Tobramycin			88	IFS	Nil
17	No	12	n.s.	Amphotericin B	Vancomycin			76	IFS	Nil
18	No	60	n.s.	Amphotericin B	Vancomycin, Cefazolin, Tobramycin			42	IFS	Nil
19	No	36	n.s.	Amphotericin B	Vancomycin, Cefazolin, Tobramycin			24	IFS	Nil
20	No	56	n.s.	Amphotericin B	Vancomycin, Cefazolin, Tobramycin			41	IFS	Nil
21	No	32	n.s.	Amphotericin B	Vancomycin			24	IFS	Nil
22	Yes	24	n.s.	Amphotericin B	Vancomycin, Cefazolin, Tobramycin			67	IFS	Nil
23	Yes	Nil	n.s.	Voriconazole	Vancomycin	PO voriconazole for 6 mths	6	24	IFS	Nil
24	No	16	n.s.	Amphotericin B 0.2g	Vancomycin 2g	IV fluconazole 0.4 g/d for 1 wk followed by PO fluconazole for 5 wks	1.5	48	IFS	Nil

25	No	n.s.	n.s.	Amphotericin B 0.1g	Vancomycin 1g	IV fluconazole 0.4 g/d for 2 wks followed by PO fluconazole 0.4 g/d for 8 wks	2.5	27	IFS	Nil
26	No	n.s.	n.s.	Amphotericin B 0.1g	Vancomycin 1g	IV fluconazole 0.4 g/d for 2 wks followed by PO fluconazole 0.4 g/d for 4 wks	1.5	24	IFS	Nil
27	No	n.s.	n.s.	Amphotericin B 0.1g	Vancomycin 1g	IV fluconazole 0.4 g/d for 2 wks followed by PO fluconazole 0.4 g/d for 6 wks	2	30	IFS	Nil
28	Yes	n.s.	n.s.	Amphotericin B 0.1g	Vancomycin 1g	IV fluconazole 0.4 g/d for 2 wks followed by PO fluconazole 0.4 g/d for 8 wks	2.5	65	IFS	Nil
29	No	n.s.	n.s.	Amphotericin B 0.1g	Vancomycin 1g	IV fluconazole 0.4 g/d for 2 wks followed by PO fluconazole 0.4 g/d for 8 wks	1.5	62	IFS	Nil
30	No	20	Palacos® R+G	Amphotericin B 0.25g	Nil	Nil	Nil	9	IFS	Nil
31	No	n.s.	Simplex P	Voriconazole 0.4g	Nil	IV caspofungin	-	-	IFS	Nil
32	No	n.s.	Synicem 1G	Voriconazole 0.6g	Nil	IV caspofungin	-	-	IFS	Nil
33	No	8	n.s.	Amphotericin B	Vancomycin	PO voriconazole for 2 mths	2	6	Failure	Amputation
34	No	48	Palacos® R	Fluconazole 2g	Nil	PO fluconazole 0.4 g/d	-	84	IFS	Nil
35	No	12	Palacos® R	Fluconazole 2g	Nil	Nil	Nil	48	IFS	Nil
36	No	36	n.s.	Voriconazole 0.4g	Gentamicin, Clindamycin	PO fluconazole 0.4g for 6 mths	6	12	IFS	Nil
37	No	24	n.s.	Amphotericin B 1.2g	Vancomycin	IV fluconazole 0.6 g/d for 8 wks followed by PO fluconazole 1 g/d for 9 wks	4	12	IFS	Nil
38	No	20	n.s.	Amphotericin B	Vancomycin	IV fluconazole 0.4 g/d for 6 wks + PO fluconazole 0.4 g/d for 12 wks	4.5	24	IFS	Nil
39	Yes	12	Palacos® R+G	Voriconazole 1g, Amphotericin B 0.25g	Gentamicin 0.5g, Vancomycin 1g	PO fluconazole for 5wks	1	72	IFS	Nil

40	No	10	n.s.	Fluconazole	Nil	Fluconazole 0.2 g/d for 47 days	1.5	17	IFS	Nil
41	Yes	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	44	IFS	Bacterial PJI
42	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	35	IFS	Nil
43	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	42	IFS	AKI
44	Yes	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	27	IFS	Nil
45	Yes	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	28	IFS	CKD dialysis
46	Yes	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	41	IFS	AKI
47	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	54	IFS	Nil
48	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	35	IFS	Dislocation
49	Yes	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	51	IFS	Nil
50	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	26	IFS	Nausea
51	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	25	IFS	Nausea
52	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	26	Failure	Persistent PJI

53	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	30	IFS	Nil
54	Yes	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	26	IFS	Nausea
55	Yes	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV Caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	39	IFS	Nil
56	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	29	IFS	Nil
57	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	37	IFS	Nausea
58	No	n.s.	Copal® G+V	Amphotericin B 0.4g	Nil	IV caspofungin 0.07g/d + PO fluconazole 0.4 g/d for 6 mths	6	35	IFS	Nil
59	No	4	n.s.	Amphotericin B 0.25g	Gentamicin	PO amphotericin B for 3wks	1	36	IFS	Nil
60	No	16	n.s.	Voriconazole 0.6g	Gentamicin, Clindamycin	PO voriconazole 0.4 g/d + PO micafungin 0.1 g/d for 1 wk followed by PO fluconazole 0.4 g/d for 12 wks	3	24	IFS	Nil
61	No	72	Palacos® R+G	Amphotericin B 0.1g	Nil	PO fluconazole 0.4 g/d followed by PO posaconazole 0.3 g/d for lifelong	Lifelong	18	IFS	Alopecia
62 -102	Yes(13) No(28)	26 (mean)	n.s.	Amphotericin B 0.1 – 0.4g	n.s.	n.s.	>4	n.s.	IFS (26/41) Failure (15/41)	PJI associated death (1) Persistent infection (5) Reinfection (10)

Palacos MV+G: medium viscosity bone cement with gentamicin Palacos R: high viscosity bone cementPalacos R+G: high viscosity bone cement with gentamicin Copal G+V: high viscosity bone cement with gentamicin and vancomycin Simplex P: dual viscosity bone cement with tobramycin Synicem 1G: high viscosity bone cement with gentamicin n.s.: not specified

Effect Measures

The primary outcome assessed in this systematic review was remission of F-PJI defined as: (i) absence of clinical signs of infection attributed to the original microorganism (relapse of infection) or a different strain (re-infection) after a minimum follow-up period of 12 months post-surgery; and (ii) no need for continuing antifungal therapy for suppressive treatment (iii) no death related to prosthetic joint infection.

Results

After searching the electronic databases, we identified 462 studies, of which 272 were duplicates and 109 studies were deemed irrelevant by title and abstract alone. Reference lists were screened, and an additional article was included. Full text evaluation led to the exclusion of 59 studies (Figure 1). Among the 25 included studies, 20 were case reports, 4 were retrospective studies and 1 was a prospective study. A total of 102 cases were included.

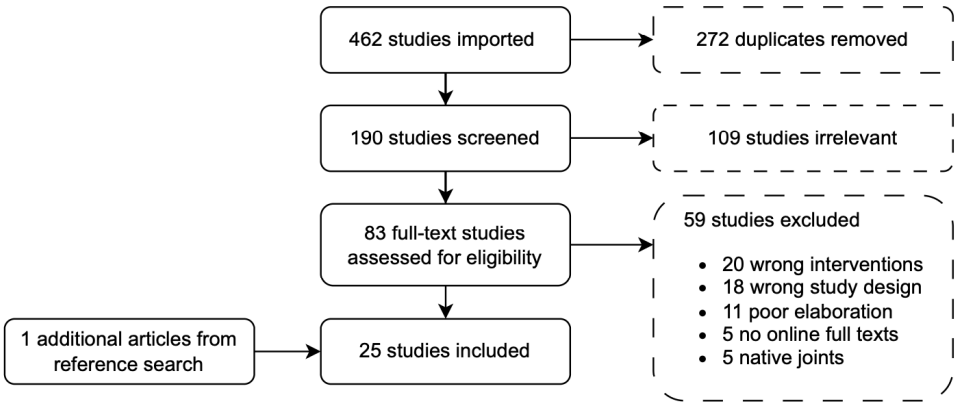

Figure1: Study selection.

General Characteristics

Of the 102 included cases, there were 34 men (33%). The mean age of patients was 71.9 years (SD 9.7, range 34-89). The joints involved were the knee in 80 (78%), hip in 20 (20%), elbow in 1 (1%) and shoulder in 1 (1%). The length of follow-up was variable with a mean of 38 months (SD 24.7, range 6 to 144).

Causative pathogen (s)

The most frequently isolated fungal pathogens were Candida parapsilosis in 56 cases (55%), followed by Candida albicans in 18 (17%), Candida glabrata in 12 (12%), Candida famata in 3 (3%), Candida tropicalis in 3 (3%), while there was one case of Candida pelliculosa, Candida utilis, Candida intertrigo, Candida rugosa, Candida species, Acremonium strictum, Alternaria infectoria, Aspergillus fumigatus, Coccidioidomycosis, Histoplasma capsulatum, Trichosporon inkin and Pichia anomala each (1%). Fungal-fungal co-infection was present in 2 cases (2%). Bacteria-fungal co-infection was present in 31 cases (30%) and the most common bacterial pathogen being staphylococcus spp. in 20 cases (65%) followed by streptococcus spp. in two (6.5%) while serratia, enterococcus, pseudomonas, klebsiella, citrobacter and escherichia in one case each (5.5%).

Bone Cements and Cement Loading

A wide variety of proprietary bone cements were used. Of the 33 cases that specified the type of bone cements used: Copal® G+V in 19 cases (58%), Palacos® MV+G in 7 (21%), Palacos® R+G in three (9%), Palacos® R in two (6%), Simplex P and Synicem 1G in one case each (3%). The remaining 69 studies did not specify the type of bone cement used (Table 3). A single antifungal agent was impregnated in bone cement in 101 cases (99%). Amphotericin B was the preferred antifungal in 88 cases (87.1%) followed by voriconazole in 12 (11.9%) and fluconazole in 3 (3.0%). Two antifungal agents were impregnated in 1 case (1%) that used a combination of voriconazole and amphotericin B. 16 cases failed to report the dose of antifungals impregnated per 40g of bone cement. The data on antifungals impregnated are summarised in Table 1.

For the 43 cases that had no bacterial co-infection, 23 (54.8%) specified that they had additional antibiotics impregnated into the bone cements. 81 cases obtained Infection-free Survival (IFS) for more than 12 months with an average follow-up of 38 months (range: 12-144). For cases that obtained IFS, AF-BCs were placed in-situ for an average of 25 weeks (range 3-60).

Discussion

Antibiotic loaded bone cements are commonly used in 2-stage resection arthroplasty for the treatment of bacteria PJIs [7]. The rarity and complexity of F-PJIs have resulted in a paucity of strong clinical evidence guiding treatment of F-PJIs. Despite the widely accepted use of AF-BCs to treat F-PJIs, there are some concerns. These include empirical treatment with limited clinical relevance to antifungal's ability to penetrate pathogen-specific biofilms; non-standardized; and unknown release kinetics [8]. A survey of 33 Australian arthroplasty surgeons in 2023 revealed that liposomal amphotericin, fluconazole and voriconazole were the common antifungals used in AF-BCs [9]. Amphotericin-B is an ideal agent to mix with bone cement due to its heat stability, broad antimicrobial spectrum and availability in powdered form. It has successfully

used in vitro and in vivo to eradicate F-PJIs even with extensive bone loss [10] Although previous research suggests a minimum dose of 0.5g per 40g PMMA to prevent Candida's biofilm formation, our review shows successful treatment of candida PJI with lower doses [11].

Voriconazole can retain its antifungal activity for at least two weeks when impregnated into bone cements and its elution rate is higher than amphotericin-B [12-14]. However, the addition of voriconazole can decrease the compressive strength of bone cements to a level unsuitable for fixation. Miller, et al. [14] were the first to investigate compressive strength in antifungal-loaded Simplex B bone cements and concluded that although the initial compressive strength for a 0.3 g/bag voriconazole formulation was above the acceptable strength for fixation, the strength decreased rapidly by the first day in elution to a strength lower than what is recommended for fixation [14,15]. However, argues that the reduced compressive strength does not depend on the elution of antifungals but on the excessive powder quantity by admixing of voriconazole in PMMA [15]. The dose recommendations for voriconazole range from 0.2g to 0.6g per 40g of PMMA cement [16].

The elution rate of antifungal bone cements is dose dependent. When antifungals are added, it increases the cement matrix porosity, which has an influence on antifungal delivery at cost of mechanical deterioration. Palacos® R cement exhibits a higher elution rate compared Simplex® P cement [14,17]. However, most studies in this review do not specify the type of bone cement used [17].

Pathogen characteristics

Fungal pathogens form biofilms on implant and tissues, showing varying tolerance to antifungal agents, with Candida albicans forming larger and more complex biofilms than other fungi pathogens [18-20]. Each fungi have its unique virulence potential, antifungal susceptibility and epidemiology [21] and limited data exists on the antifungal concentrations needed to achieve minimum biofilm eradication concentration (MBEC) for each pathogen [22]. In our review, most F-PJI cases with bacterial super-infections had antibiotic added to the bone cement spacer. When compared to pure AF-BC, the success rates were slightly lower but the reason for this is unclear.

The ideal interval between implant removal and reimplantation for F-PJIs is unknown as fungal pathogens are notoriously indolent. In our review, the mean interval was 25 weeks (range 4-68 weeks). Differentiating successful eradication from persistent PJI using serologic tests is challenging [2]. Although Wang, et al [23] propose that reimplantation should only be performed in the absence of clinical signs and symptoms with CRP and ESR within the normal range [23], our group challenges this notion on the basis that fungal infections are commonly associated with normal inflammatory markers [24].

Elution Rate

The elution rate of AF-BC is influenced by the addition of poragen and the formulation of the antifungal. Kweon et al. reported that adding 10g of cephazolin to AF-BC improved the elution rate of amphotericin B by seven times. Other antibiotics like vancomycin, tobramycin, meropenem, gentamicin and clindamycin were identified in our study as additions for treating F-PJIs without bacterial co-infection [25].

The formulation of amphotericin influences its elution rate when used in bone cements. A comparison between liposomal and deoxycholate amphotericin B revealed that the liposomal formulation had better elution rates. Another study explored an alternative non-liposomal formulation, N-methyl-D-glucamine/palmitate amphotericin B, which exhibited a higher elution rate than deoxycholate amphotericin B [26]. However, our review lacked clear descriptions on the form of amphotericin B used in the identified studies to comment on these differences [11].

Limitations and Strengths

Our study faced limitations due to the lack of high-quality evidence regarding the benefits of AF-BCs. Our study identified case reports, retrospective studies and prospective studies with a notable absence of long-term prospective studies evaluating the effectiveness of AF-BCs in treating F-PJIs. While many reported cases had long-term follow-ups, there was inadequate documentation of the progress of the follow-ups often with only the end-outcome being reported. Our study also showed high success rates in the treatment of fungal prosthetic joint infection, but registry data paints a bleaker picture. This raises concerns about publication bias, skewing our perception of success rates in published literature [4].

Additionally, there was a lack of documentation on the treatment protocol such as the type of bone cement used and the form and dose of antifungals, thereby limiting our ability to draw conclusions on the most effective combination for antifungal impregnated bone cements. Another issue noted include the lack of sufficient studies to analyse the effectiveness of AF-BC equally across four different joints. We acknowledge that the principle of fixing joint prosthesis, the implant-cement-bone interface and the antifungal-cement filling agent system are similar irrespective of the joints. The review noted most of the case reports involving a Total Knee Arthroplasty (TKA), with the next majority being a total hip arthroplasty and only a case reported each for total elbow and shoulder arthroplasty. Therefore, the findings of the review are a more accurate representation of the efficacy of AF-BC in patients who previously had a TKA.

The lack of consistency or specific treatment guidelines of AF-BC continue to pose a problem in the decision-making prior to reimplantation. Several criteria to consider include the type, dosage and form of anti-fungal to be added into the bone cement. Our review showed that the concentration of anti-fungal additive ranged between 0.1g to 1g per 40g of bone cement, either the powdered or liposomal form could be considered. However, the lack of randomised controlled trials makes the selection of antifungals in bone cements a difficult endeavour even for experienced orthopaedic surgeons. Despite the limitations, our review managed to have an in-depth analysis and breakdown of the case studies. We captured specific AF-BC concentrations and duration and dosage of adjunctive systemic therapy for each case, to identify a potential pattern in the treatment methods. To the best of our knowledge,

this systematic review is the most comprehensive summary of reported use of antifungals in bone cements. A recent publication in July 2022 by Anagnostakos, et al. [27] also reviewed the efficacy of AF-BC in F-PJI but concluded that further evaluation of this subject matter is still required [27-51].

Conclusion

In conclusion, our systematic review showed that a 2-stage reimplantation approach using AF-BCs alongside systemic antifungal therapy was successful in treating majority of F-PJIs. Based on the information gathered, the most effective anti-fungal identified was the liposomal Amphotericin B (0.37±0.25g, range 0.1-1.2g per 40g of bone cement) with subsequent use of systemic antifungal therapy for at least 6 months.

Authors Contributions

All authors contributed to the study design, provided thorough feedback, and gave final approval of the version to be published. W.P.J.T and A.T.G.M analysed the data and designed the figures and tables. All authors can take responsibility for the integrity and accuracy of the data analysis.

Competing Interests

We declare that there is no potential conflict of interest and that no funding was provided in this research.

Ethical Statement

Not applicable.

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