



■ ARTHROPLASTY

Three-stage revision arthroplasty for the treatment of fungal periprosthetic joint infection: outcome analysis of a novel treatment algorithm

A PROSPECTIVE STUDY

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Aims

Fungal periprosthetic joint infections (fPJIs) are rare complications, constituting only 1% of all PJIs. Neither a uniform definition for fPJI has been established, nor a standardized treatment regimen. Compared to bacterial PJI, there is little evidence for fPJI in the literature with divergent results. Hence, we implemented a novel treatment algorithm based on three-stage revision arthroplasty, with local and systemic antifungal therapy to optimize treatment for fPJI.

Methods

From 2015 to 2018, a total of 18 patients with fPJI were included in a prospective, single-centre study (DKRS-ID 00020409). The diagnosis of PJI is based on the European Bone and Joint Infection Society definition of periprosthetic joint infections. The baseline parameters (age, sex, and BMI) and additional data (previous surgeries, pathogen spectrum, and Charlson Comorbidity Index) were recorded. A therapy protocol with three-stage revision, including a scheduled spacer exchange, was implemented. Systemic antifungal medication was administered throughout the entire treatment period and continued for six months after reimplantation. A minimum follow-up of 24 months was defined.

Results

Eradication of infection was achieved in 16 out of 18 patients (88.8%), with a mean follow-up of 35 months (25 to 54). Mixed bacterial and fungal infections were present in seven cases (39%). The interval period, defined as the period of time from explantation to reimplantation, was 119 days (55 to 202). In five patients, a salvage procedure was performed (three cementless modular knee arthrodesis, and two Girdlestone procedures).

Conclusion

Therapy for fPJI is complex, with low cure rates according to the literature. No uniform treatment recommendations presently exist for fPJI. Three-stage revision arthroplasty with prolonged systemic antifungal therapy showed promising results.

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Introduction

Fungal periprosthetic joint infections (fPJIs) are rare but severe complications of total hip arthroplasty (THA) and total knee arthroplasty (TKA). While many publications and therapy regimens for bacterial periprosthetic

joint infections (PJI) exist, treatment approaches for periprosthetic fungal infections remain at a very early stage. Diagnosis is often delayed, because fPJI are difficult to detect,¹ resulting in a time-lapse before sufficient therapy is initiated. Individual case

Table 1. Patient baseline parameters and demographics.

Variable	Patient data (n = 18)
Age, yrs, mean (SD); range	72.8 (10.2); 56 to 85
Female sex, n (%)	10 (55.5)
BMI, kg/m ² , mean (SD); range	27.9 (6.1); 20 to 38
ASA score, median (SD); IQR	3 (0.78); 2 to 3.5
Previous surgeries, median (SD); IQR	4 (1.98); 3 to 5
CCI, median (SD); IQR	6 (3.1); 2.25 to 8
Left side, n (%)	11 (61.1)
THA, n (%)	11 (61.1)
Smoker, n (%)	3 (16.6)

ASA, American Society of Anaesthesiologists; CCI, Charlson Comorbidity Index; IQR, interquartile range; SD, standard deviation; THA, total hip arthroplasty.

series, describing various surgical and antifungal therapies, have been reported in the literature.²

It is important to differentiate between therapy approaches, such as debridement, antibiotics and implant retention (DAIR), and one-, two-, or multiple-stage procedures. However, no evidence has been published indicating the superiority of any approach to date. Furthermore, results, as well as the choice of antimycotic agents and the duration of antifungal therapy, differ substantially among various treatment protocols in literature.²

According to the PRO-IMPLANT Foundation (Germany) treatment algorithm, we performed a three-stage revision in combination with long-term systemic antifungal therapy.³ This study aimed to analyze the outcomes of this revision approach as it relates to the paramount objective of septic revision arthroplasty - permanent infection control.

Methods

From 2015 to 2018, 623 patients with acute or chronic PJI following TKA or THA were treated in a high-volume infection referral centre. Overall, 20 patients (3.1%) were diagnosed with a chronic fPJI. A total of 18 patients (2.8%) were included in a prospective, single-centre cohort study. In all, eight patients developed fPJI after TKA, and 12 after THA. Two patients with fPJI were treated with long-term suppression due to comorbidity. As a three-stage procedure was not completed, these two patients were not included in the study. Each case intended for a three-stage revision was discussed in a multidisciplinary team (MDT). All 18 patients gave their consent to be treated according to the PRO-IMPLANT Foundation algorithm. Due to the rarity of the diagnosis, no further exclusion criteria were constituted. A minimum follow-up of 24 months was defined. The baseline parameters are shown in Table 1.

The definition of PJI was based on the European Bone and Joint Infection Society (EBJIS) criteria.⁴ To provide microbiological evidence of PJI, McNally et al⁴ defined a single positive sample as “likely infection” for uncommon contaminants (e.g. fungal pathogens). Therefore, a single positive tissue sample was sufficient, as well as microbiological evidence of fungal infection based on analyses of preoperative joint aspiration or sonication fluid for the diagnosis of fPJI.

In the microbiological laboratory, samples were prepared using forceps and scalpel under laminar air flow. Aliquots of the tissue were subsequently placed on different aerobic and anaerobic culture plates, and growth media (blood agar, chocolate agar, Schaedler agar, brain-heart infusion, and Wilkins-Chalgren infusion). Culture was performed under human body temperature conditions (37 °C) for 14 days.

All removed orthopaedic devices were treated in an ultrasonic bath (Bandelin, Germany), sonicate fluid was incubated in blood culture bottles and conventional culturing was performed eventually. Sensitivity and specificity were determined using two-by-two contingency tables.

The primary outcome was defined as successful eradication of infection according to the consensus criteria developed by Diaz-Ledezma et al:⁴ 1) healed wound condition; 2) no infection-related local revision surgery; and 3) absence of PJI-related mortality. Therapy failure was determined as revision owing to septic complications, such as persistent or newly developed PJI. The secondary outcome measure was defined as reimplantation of a prosthesis. The functional outcomes, as measured at the latest follow-up, were included.

Statistical analysis. Data analysis was performed using the Statistical Package for Social Sciences Software (IBM SPSS Statistics version 24; IBM, USA). Descriptive statistical results (mean, median, standard deviation, range, interquartile range and percentage) were recorded to describe comorbidities, complications, and revisions. If a median is stated, the 25th and 75th percentiles are specified in brackets as the interquartile range (IQR). Statistical analysis was performed using Kaplan-Meier estimates and survival curves. The Shapiro-Wilk test was performed to determine normality. Subgroups were compared with the Mann-Whitney U test for non-parametric analysis. Comparative analysis was performed using chi-squared tests for categorical data. The significance level was set at $p < 0.05$.

Three-stage revision procedure. Treatment of fPJI was performed according to the recommendations of the PRO-IMPLANT Foundation.³ The principles of this algorithm include, but are not limited to, the following key points: no drug holidays prior to reimplantation of the prosthesis; no joint aspiration before reimplantation; biofilm-active therapy only after reimplantation; and

Table II. Local antifungal therapy.

Cement	Amphotericin B (liposomal), g	Voriconazole, g	Gentamicin, g	Vancomycin, g
Spacer	0.4	0.4	0.5 to 1	2
Fixation cement	0.2	0.2	0.5	2

Values per 40 g bone cement (polymethylmethacrylate), according to the PRO-IMPLANT Foundation.³

antimicrobial therapy for 12 weeks from the date of last positive microbiological evidence (six months for fungal agents). The three-stage exchange procedure must not alter the predetermined interval of six weeks from explantation to reimplantation.

A three-stage revision procedure should be reserved for difficult-to-treat microorganisms (e.g. rifampicin-resistant staphylococci, ciprofloxacin-resistant gram-negative bacteria, and fungi) due to a lack of any effective, biofilm-active treatment option.

In cases of positive preoperative joint aspiration, evidence of fPJI was provided and prosthesis explantation was conducted, combined with extensive debridement and removal of all foreign bodies, and insertion of a custom-made amphotericin B-loaded polymethylmethacrylate (PMMA) spacer.

A scheduled revision was performed three weeks after the index surgery to trigger two key factors for successful treatment of fPJI: additional meticulous debridement to reduce the local burden of fungi; and exchange of the amphotericin B loaded spacer, to ensure continuously high local concentrations of antimycotic agents.⁵

If fPJI was not detected preoperatively but bacterial PJI was presumed, a vancomycin/gentamicin loaded spacer (COPAL G+V; Heraeus, Germany) was used within the context of a two-stage revision procedure. With detection of microbiological evidence of fPJI in the tissue samples or sonication fluid, revision was scheduled with a switch to an amphotericin B-loaded spacer after three weeks.

As there is no industrial bone cement available, containing antimycotic agents, liposomal amphotericin B was added to commercial bone cement containing vancomycin/gentamicin (COPAL G+V). We added 0.4 g liposomal amphotericin B per 40 g spacer cement, and 0.2 g amphotericin to the fixation cement (Table II). Liposomal amphotericin B results in improved elution compared to regular amphotericin B.⁶ Postoperatively, a course of intravenous antifungal therapy was initiated with a loading dose of 70 mg caspofungin, which was reduced to 50 mg for patients weighing less than 80 kg from the day after the operation. In cases of an uneventful postoperative period with regular wound healing, antifungal medication was switched to oral administration of 400 mg fluconazole/day. The total duration of antifungal therapy after reimplantation was six months. During that time, outpatients presented once a month and laboratory tests were conducted. In cases of polymicrobial

mixed infections, additional biofilm-active antimicrobial therapy was administered.³

Results

From 2015 to 2018, a total of 18 patients were included in the single-centre study. The median American Society of Anesthesiologists (ASA) physical status classification score was three (IQR 2 to 3.5). The median Charlson Comorbidity Index (CCI) was seven (IQR 2.25 to 8). The diagnosis of fPJI was confirmed by positive preoperative joint aspiration in two patients, and intraoperative tissue samples in 16 patients. Following the EBJS criteria, a “confirmed infection” was diagnosed in 13, a “likely infection” in five patients.

Polymicrobial infections with proof of bacterial and fungal involvement were detected in seven cases (Table III). The medical history of the cohort showed at least one failed exchange procedure, due to chronic PJI with a median of four operations (IQR 3 to 5) prior to hospital admission.

Four patients presented with a fistula and three patients with a soft tissue defect, requiring additional reconstructive surgery. All patients showed microbiological evidence of PJI, and suffered from specific complaints due to chronic PJI with a relevant loss of quality of life.

The mean follow-up was 35 months (25 to 54). In all, 16 patients (88.8%) maintained revision-free survival, as defined by the consensus criteria by Diaz-Ledezma et al.⁷ The follow-up details are presented in Table IV and the Kaplan-Meier estimator in Figure 1. At the latest follow-up, one patient required an additional two-stage revision owing to a bacterial PJI. One patient deceased due to septic multi-organ failure despite carrying out a Girdlestone resection arthroplasty as an emergency procedure. No patient was lost to follow-up.

In 13 patients (72.2%), revision joint arthroplasty was performed after a mean of 119 days (55 to 202). In two patients, permanent Girdlestone resection arthroplasty was performed, and three patients received a cementless, modular knee arthrodesis as a salvage procedure. A detailed MDT audit was preceded for the selection of any salvage procedure.

Overall, 17 patients received a regular postoperative course of oral fluconazole from day ten and for another six months after reimplantation. Antifungal therapy was initiated with the intravenous administration of caspofungin. Fluconazole-resistant *Candida albicans* was

Table III. Antimicrobial findings.

Patient no*	Preoperative joint aspiration†	Explantation (n)‡	Scheduled revision (n)‡	Reimplantation (n)‡§
1	<i>Staphylococcus epidermidis</i>	<i>Candida famata</i> (2/6) <i>S. epidermidis</i> (2/6)	Culture negative (0/5)	Culture negative (0/5)
2	<i>Candida parapsilosis</i>	<i>C. parapsilosis</i> (2/9)	Culture negative (0/5)	Culture negative (0/3)
3		<i>Candida albicans</i> (2/4)	<i>C. albicans</i> (1/3)	Culture negative (0/5)
4		<i>Candida famata</i> (3/9) <i>Citrobacter koseri</i> (9/9)	<i>C. famata</i> (2/5)	Culture negative (0/5)
5		<i>Candida tropicalis</i> (1/4) <i>S. epidermidis</i> (2/4)	Culture negative (0/4)	Culture negative (0/3)
6		<i>Candida parapsilosis</i> (1/4) <i>Staphylococcus caprae caprae</i> (3/4)	Culture negative (0/4)	Culture negative (0/5)
7		<i>C. albicans</i> (1/4)	<i>C. albicans</i> (3/3)	Culture negative (0/5)
8		<i>C. parapsilosis</i> (2/6)	Culture negative (0/3)	Culture negative (0/7)
9		<i>Candida glabrata</i> (2/7) <i>Escherichia coli</i> (4/7)	Culture negative (0/7)	Culture negative (0/7)
10	<i>C. famata</i>	<i>C. famata</i> (1/4)	Culture negative (0/4)	Culture negative (0/3)
11		<i>C. parapsilosis</i> (1/3)	Culture negative (0/5)	Culture negative (0/3)
12		<i>C. albicans</i> (2/5)	Culture negative (0/4)	Culture negative (0/3)
13		<i>C. albicans</i> (3/5)	<i>C. albicans</i> (3/4)	Culture negative (0/4)
14		<i>S. epidermidis</i>	<i>C. albicans</i> (1/5) <i>S. epidermidis</i> (3/5)	<i>C. albicans</i> (3/4)
15		<i>C. parapsilosis</i> (2/5) <i>Streptococcus sanguinis</i> (5/5)	Culture negative (0/3)	Culture negative (0/7)
16		<i>C. albicans</i> (1/7)	Culture negative (0/5)	Culture negative (0/5)
17		<i>Alternaria infectoria</i> (2/5)	Culture negative (0/5)	Culture negative (0/6)
18		<i>C. albicans</i> (1/4)	Culture negative (0/3)	Culture negative (0/4)

*Patients 2 and 10 received an amphotericin B spacer during the first operation.

†Only positive results listed.

‡First number within parentheses indicates positive test results; second number indicates the absolute number of samples collected.

§Patients 7, 9, and 13 received a cementless modular arthrodesis; patients 12 and 15 underwent a Girdlestone procedure.

Table IV. Therapy protocol.

Patient no.	Entity	Age, yrs	CCI	Previous surgeries*	Clinical feature	Reconstructive surgery	Follow-up, mnths	Complication	Primary outcome	Secondary outcome
1	THA	85	10	2			44	Bacterial PJI after 24 months	Two-stage exchange†	rTHA
2	TKA	66	2	1			35	None	IFS	rTKA
3	THA	81	9	3			42	AKI	IFS	rTHA
4	THA	67	2	3			27	None	IFS	rTHA
5	TKA	81	8	5			28	CKD dialysis	IFS	rTKA
6	THA	81	7	1	Fistula		41	AKI	IFS	rTHA
7	TKA	56	1	5	Soft-tissue defect	Gastrocnemius flap	54	None	IFS	Cementless KA
8	THA	78	7	1	Fistula		35	Dislocation (closed reduction)	IFS	rTHA
9	TKA	66	5	6	Soft-tissue defect	Anterolateral thigh flap	51	None	IFS	Cementless KA
10	THA	81	10	5			26	Nausea	IFS	rTHA
11	TKA	57	2	4			25	Nausea	IFS	rTKA
12	THA	82	7	7	Fistula		26	Persistent PJI	Patient deceased	Girdlestone
13	TKA	79	9	4	Soft-tissue defect	Gastrocnemius flap	30	None	IFS	Cementless KA
14	THA	78	3	3			26	Nausea	IFS	rTHA
15	THA	60	8	7	Fistula		39	None	IFS	Girdlestone
16	TKA	71	8	4			29	None	IFS	rTKA
17	THA	83	7	3			37	Nausea	IFS	rTHA
18	THA	57	3	6			35	None	IFS	rTHA

*Primary arthroplasty was defined as index surgery (0).

†Successful treatment after two stage-exchange.

AKI, acute kidney injury; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; IFS, infection-free survival; KA, knee arthrodesis; PJI, periprosthetic joint infection; rTHA, revision total hip arthroplasty; rTKA, revision total knee arthroplasty; THA, total hip arthroplasty; TKA, total knee arthroplasty.

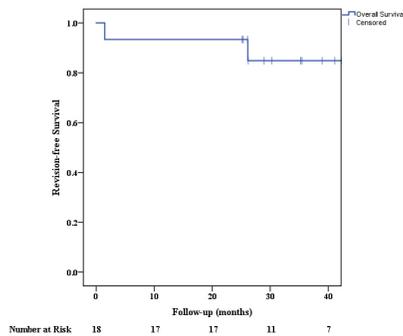


Fig. 1
Kaplan-Meier survival estimates.

At the last follow-up examination, nine out of 13 patients with revision joint arthroplasty were able to walk independently. Three patients used forearm crutches and reported a mean daily walking distance of about 500 metres. One patient reported sufficient mobility for short distances at home. One patient with a permanent Girdlestone situation was able to transfer from the bed to a wheelchair independently, but could not walk short distances without major limitations. The other patient subjected to a Girdlestone procedure was immobile and subsequently died due to multiorgan failure. All three patients with knee arthrodesis depended on the use of forearm crutches, and were able to walk short distances

Table V. Literature on fungal periprosthetic joint infections.

Reference	Patients, n	Period	Surgical procedure	Follow-up, mths	Infection eradication, %
Garcia-Oltra et al 2011 ¹⁰	3	2002 to 2010	DAIR	31	0
			Two-stage revision	31	28
Anagnostakos et al 2012 ¹¹	7	2004 to 2009	Two-stage revision Fluconazole, six weeks postoperatively	28	100
Ueng et al 2013 ¹²	7	2000 to 2010	Two-stage revision	31	28
Geng et al 2016 ¹³	8	2000 to 2012	Two-stage revision Fluconazole, six weeks postoperatively	53	77.5
Ji et al 2017 ⁹	11	2004 to 2014	One-stage revision	60	63
Kuo et al 2018 ¹⁴	29	1999 to 2014	DAIR	60	28.6
			One-stage revision	60	33.3
			Two-stage revision	60	46.3
Gao et al 2018 ¹⁵	17	2000 to 2015	Two-stage revision	65	72.2
Escola-Verge et al 2018 ¹⁶	20	2003 to 2015	DAIR		27
	15		Implant revision		67
Kim et al 2018 ¹⁷	9	2001 to 2016	Two-stage revision		100
Brown et al 2018 ¹⁸	31	1996 to 2014	DAIR, one- and two-stage revision	24	55
Theil et al 2019 ¹⁹	26	2009 to 2017	Two-stage revision	33	38.5
Current Study	18	2015 to 2019	Three-stage revision Fluconazole, six months postoperatively	25	88.8

DAIR, debridement, antibiotics and implant retention.

detected in one patient. As no appropriate oral antimycotic therapy was available, outpatient parenteral antibiotic therapy (OPAT) with caspofungin was initiated for six months.⁸ Seven patients with confirmed polymicrobial bacterial and fPJIs received additional antibacterial therapy, starting from the day of explantation. A biofilm-active antimicrobial agent was administered for six weeks after reimplantation.³

Adverse reactions, due to long-term antimicrobial and antifungal therapy, were monitored on a regular basis. Two patients showed signs of acute kidney injury. One patient developed chronic kidney disease, with the need for intermittent haemodialysis. During outpatient presentation, four patients complained about nausea. The blood tests during routine monitoring showed no remarkable pathological findings. One patient was readmitted after early postoperative THA dislocation. Conservative treatment was initiated after closed reduction.

without technical aids.

Discussion

Implementing standardized treatment algorithms for PJI has led to a significant improvement of the outcome in this integral aspect of orthopaedic surgery.^{3,9} The principles of treatment for bacterial PJI cannot be equated with those for fPJI owing to the differences in difficult-to-treat fungal organisms, lower levels of traceability, and a lack of relevant expertise.¹ Treatment algorithms for fPJI are a hot topic with only marginal evidence available at present. Different surgical and antifungal therapy regimens show divergent results, which emphasizes the need for further investigations (Table V).

The scope of our study was to contribute scientific data to the controversial discussion on definition and modern treatment algorithms in the field of fPJI. Literature

does not show any superiority of either approach (one-, two-, or three-stage). Hence, our presented data suggest the effectiveness of this procedure, in particular after multiple revisions before. A three-stage procedure is burdensome, but the value of a best possible outcome should be considered higher than the potential stress of one additional scheduled revision compared to two-stage revisions. Due to the risk of false negative samples, especially in the treatment of difficult-to-treat organisms (such as fungi), and the lack of a reliable intraoperative assessment for those, it is a paramount objective of the three-stage approach to minimize the risk of persistent fungal colonisation that lead to therapy failure. This safety for all patients must be counterbalanced with potentially one odd operation for only some patients.

As this was a short-term study, the follow-up seems comparable to other studies.¹⁸ The recruitment interval from 2015 to 2018 was shorter than that of other studies. Therefore, regular outpatient presentation should be established to ensure continuous re-evaluation.

Diagnosis of fPJI can be exceedingly difficult, particularly during the early stages of disease, and requires a thorough work-up. Patients often complain about only few symptoms, similar to those of low-grade PJI.¹⁶ Patients with several comorbidities are particularly susceptible to fPJI.¹³ Various risk factors have been identified, such as immunosuppression, obesity, diabetes, number of previous revision surgeries, as well as long-term antibiotic treatment.^{2,13} Analyses of the baseline parameters of the patients in the present study support these findings.

The literature shows a high rate of mixed bacterial and fungal PJIs, which impede the effects of appropriate diagnostics and consistent therapy. These findings are consistent with the results of the present study. Therefore, preoperative joint aspiration should be mandatory during the first diagnostic examination if bacterial or fungal PJI is presumed. Mixed infections are associated with markedly worse outcomes in the literature. Sidhu et al²⁰ reported a revision-free survival rate of 38% among patients with mixed bacterial infections. In contrast, only one treatment failure occurred in the mixed infections cohort of this study. It is assumed that the additional antimicrobial, biofilm-active therapy was highly effective,³ but we are aware that these are only short-term follow-up results.

The spectrum of fungal pathogens detected in the present study was comparable with that of previous publications, particularly the frequency of infections with *Candida albicans* and *Candida parapsilosis*.²¹ Infections with mould fungal species, as we observed in one patient with *Alternaria infectoria*, are rare and have only been reported in two previous case studies.²²

No uniform treatment recommendations or diagnostic standards exist for fPJI. The International Consensus Meeting on Musculoskeletal Infection 2018 (Philadelphia,

USA) discussed fPJI in four questions, with low evidence and vague therapy recommendations.²³ The recently published EBJIS definition by McNally et al⁴ facilitates the use of defined criteria in a consistent algorithm.⁴ Accordingly, a single positive microbiological sample of an uncommon or highly virulent organism should be considered as a likely infection. Contamination with these pathogens is unlikely and the consequences of a missed infection might be devastating. In accordance, the PRO-IMPLANT Foundation categorizes fungal agents as highly virulent, though with a comparably low level of evidence.³

The overall need for a future precise, well-accepted definition of fPJI must be emphasized. An important step in this direction was made by publication of the EBJIS criteria for PJI definition.⁴ We acknowledged that the lack of evidence concerning generally adopted definition criteria for fPJI is a limitation of the present study.

Currently, neither refined diagnostic techniques, nor any other tools, are available to improve the determination of fPJI. In future investigations, process sequencing of the internal transcribed spacer segment, for fungal pathogens specifically, could enhance the diagnostic capability.²⁴

Unlike for bacterial PJI, there are no histological standards defined for either classification of fPJI. The histopathological criteria for bacterial PJI, established by Morawietz et al²⁵ are not explicitly defined for fPJI. It remains unclear whether histological observations about bacterial infections can be applied to fungal infections.²³ For this reason, histology was no dedicated focus of our study protocol, although this feature might be of interest for further investigations.

Antimicrobial therapy as a cornerstone of successful PJI treatment is indispensable in every treatment algorithm.³ However, recommendations regarding the appropriate duration differ and can range from six to 52 weeks.²⁶ Meta-analyses have identified improved eradication of infection with prolonged systemic therapy from three to six months.¹² This is consistent with our findings, which showed high rates of eradication following six months of antifungal treatment after three-stage revision arthroplasty.

The second key factor of antifungal treatment, besides systemic therapy, is adequate local therapy. When adding antifungal agents to the bone cement mixture, certain characteristics must be considered. The mixing ratio for bone cement differs among spacers and the cement used during reimplantation. High drug doses affect the mechanical stability of PMMA, particularly if two or more drugs are used. At the time of revision arthroplasty, antibiotics should not comprise more than 10% to 15% of the cement mass.³ The lower dose of added antimycotics and the third-generation cementing technique for the fixation cement result in superior mechanical properties.⁵

Considering the microbiological findings, as well as the point in time at which the fPJI diagnosis was made, it became clear that if a fungal infection was diagnosed preoperatively and an antimycotic PMMA spacer was used initially, no persistent infection (0%) was detected in subsequent operations. In the event that fPJI was diagnosed in tissue samples acquired during explantation without preoperative diagnosis of fungal infection, and implantation of a spacer without antifungal agents during the index operation, fPJI was detected in five of 16 (31.2%) spacer exchanges (Table III). However, due to the small study group that difference was not significant ($p = 0.51$, Fisher's exact test).

The overall importance of systemic and local antifungal therapy is underlined in the present study, which is consistent with the findings of previous studies.¹ Furthermore, the present findings reveal the essential advantage of a three-stage revision strategy. Repeated surgical debridement, combined with a scheduled spacer exchange, could facilitate continuous delivery of the highest local drug concentrations with optimized release kinetics and without systemic side-effects.⁵ Furthermore, certain disadvantages may be associated with a three-stage procedure, such as increased perioperative and postoperative risks, including mortality and adverse drug effects, due to prolonged antifungal and antibacterial therapy. Indications for additional scheduled surgery must be justified by evidence of improved outcomes compared with those of one- or two-stage procedures.^{14,18} Depending on the antimicrobial therapy prescribed, advanced outpatient care is required to monitor potential complications.

Indications for any salvage procedure were closely evaluated by a MDT and confirmed after a detailed explanatory meeting and risk assessment regarding the outcome.²⁷ Salvage therapy should only be considered in cases of high perioperative risks or patient refusal of an eradication strategy. First-line salvage therapy in patients with chronic fPJI, in our opinion, must be long-term antifungal suppression with fluconazole or voriconazole.³ The establishment of a persistent fistula should be the last option.²⁷

Knee arthrodesis was only performed in case of complete insufficiency of the extensor apparatus, in combination with an extensive compromise of the soft tissue envelope and additional reconstructive surgery for soft tissue coverage.

A permanent Girdlestone situation only was feasible if immobility must be tolerated, had previously existed, or the patient denied consent to further surgical treatment. The latter is the case in the investigated cohort. Both Girdlestone patients denied further multiple-stage revision for personal reasons.

There are limitations to the current study. Foremost, cohorts investigating fungal PJI are limited by patient numbers. We identified 18 patients, thus the strength of

the data may be weakened. However, this study is one of the largest cohorts reported with a standardized treatment algorithm for fungal PJI.

Following the EBJIS criteria, we considered one positive sample to be sufficient for a likely infection.⁴ The lack of generally accepted guidelines concerning diagnosis and treatment of fPJI must be emphasized. The focus was to evaluate the rate of successful infection eradication. Patient-reported outcome measures need to be addressed in further investigations.

In conclusion, treatment of fPJI is a challenge that requires a multidisciplinary standardized team approach with individual case analyses for optimized outcomes. Three-stage revision arthroplasty, combined with local and systemic antifungal therapy, shows promising results and is associated with high revision-free survival rates in a short-term follow-up. Long-term results are necessary to confirm the present findings.



Take home message

- Therapy for fungal periprosthetic joint infection (fPJI) is complex, with low cure rates according to the literature.
- No uniform treatment recommendations presently exist for fPJI.

fPJI.

- Three-stage revision arthroplasty with prolonged systemic antifungal therapy showed promising results.

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