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Difficult to treat: are there organism-dependent differences and overall risk factors in success rates for two-stage knee revision?

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Abstract

Objectives Failure after two-stage procedure for periprosthetic joint infection (PJI) is a rare, but devastating complication. Some authors assume a correlation of underlying organisms and recurrence rate. Methicillin-resistant Staphylococci (MRS) and other organisms (quinolone-resistant Gram-negative bacteria, rifampicin-resistant *Staphylococcus*, *Enterococcus*, and *Candida*) are meant to be “difficult to treat” (DTT) with an inferior outcome for two-stage revision. In addition to the type of bacteria, some more risk factors seem to be present. The aim of this study was (1) to detect a difference of reinfection rates between reinfection-causing groups of bacteria [“difficult to treat” (DTT), “easy to treat” (ETT) and methicillin-resistant staphylococci (MRS)] after a two-stage procedure, and (2) find overall risk factors for reinfection in a standardized long (spacer insertion for at least 6 weeks) two-stage procedure for periprosthetic knee infection.

Methods One hundred and thirty-seven two-stage revisions for periprosthetic knee infection were performed at one tertiary referral center. Finally, 96 patients could be included for analyses. Possible risk factors (comorbidities, prior surgery, etc.) and the types of organisms were documented. Quinolone-resistant Gram-negative bacteria, rifampicin-resistant *Staphylococcus*, *Enterococcus*, and *Candida* were classified as “difficult to treat” (DTT). Methicillin-resistant Staphylococci were summarized as “MRS”, all other organism are summarized as “easy to treat” (ETT). Statistical analyses included univariate analysis (*t* test, Fisher’s exact test, Chi square test) and logistic regression analysis.

Results There were no statistical significant differences in recurrent infection rates between organism groups (DTT vs. ETT, $p=0.674$; DTT vs. MRS, $p=0.705$; ETT vs. MRS, $p=0.537$). Risk factors seem to be “need of revision after first stage” ($p=0.019$, OR 5.62) or completed second stage ($p=0.000$, OR 29.07), numbers of surgeries ($p=0.028$) and alcohol abuse ($p=0.019$, OR 5.62).

Conclusions Revision needed during or after a two-stage exchange, numbers of surgeries and alcohol abuse are risk factors for recurrence, a different recurrence rates between organism-groups cannot be shown. The absence of significant differences in recurrence rates points to the importance of the individuality of each periprosthetic infection case: a reduction of necessary surgeries (with a thorough debridement, appropriate antibiotic addition to spacers) and the control of comorbidities (alcohol abuse) appear to be essential components of a two-stage exchange.

Keywords Periprosthetic infection · Difficult to treat · Two-stage exchange · Revision TKA · Methicillin-resistant *Staphylococcus aureus* · Two stage knee revision

Introduction

Periprosthetic joint infection (PJI) after total knee arthroplasty (TKA) is a devastating complication and is associated with significant morbidity and high socioeconomic costs [1–4]. A two-stage protocol with the temporary insertion of an antibiotic-laden spacer is, among other therapy options, one of the most promising pathways [5, 6]. Recurrence of infection after two-stage revision occurs in up to 19% [7–9] which elucidates the socioeconomic and individual burden of PJI. Recent studies [10, 11] showed risk factors for recurrent infection after failed two-stage revision. Some authors [11–14] suspected different bacteria (methicillin-resistant staphylococci, rifampin-resistant staphylococci, enterococci,

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fungi, fluorquinolone-resistant Gram-negative bacteria) for an inferior outcome (outcome: "infection free").

The hypothesis of the study is (1) that the "difficult to treat"-bacteria postulated by Trampuz et al. [15] are more difficult to eradicate and thus a higher recurrence rate occurs and (2) that there are other independent risk factors (comorbidities) for recurrence in a standardized long (spacer insertion for at least 6 weeks) two-stage procedure for periprosthetic knee infection.

Materials and methods

The study received IRB approval by the institutional review board at the authors' institution, patients signed the informed consent. The current study is a retrospective review of 137 two-stage revisions for periprosthetic knee infection performed at one tertiary referral center between 2002 and 2010. Twenty-three patients had to have excluded due to another prior two-stage revision. 114 patients were followed up: 6 patients were lost to follow-up; 12 patients showed a too short follow up (< 24 months) at the time-point of conducting the study. 96 patients could be included for analyses.

Patient demographics including age, gender, BMI, health status (American Society of Anesthesiologists Classification, ASA), comorbidities (diabetes mellitus, arterial hypertension, peripheral artery disease, coronary heart disease, chronic heart failure, chronic kidney failure, chronic obstructive pulmonary disease, smoking, alcohol abuse, drug abuse, malignancies), possible risk factors and clinical and operative characteristics (numbers of surgeries, presentation of fistula prior to two stage procedure, need of spacer change during two stage protocol, use of antibiotic-containing bead chains, sort of antibiotic laden cement in spacers, revision needed during two-stage procedure, revision needed after two-stage procedure, duration of inserted spacer, sort of oral antibiotics) were recorded. The American Society of Anesthesiologists (ASA) physical status classification score was used as a proxy variable for health status. The types of organisms and sensitivities were documented for all procedures. Quinolone-resistant Gram-negative bacteria, rifampicin-resistant *Staphylococcus*, *Enterococcus*, and *Candida* [12] were classified as "difficult to treat" (DTT). Methicillin-resistant Staphylococci were summarized as "MRS", all other organism (including culture-negative infections and poly-microbial infection without above-mentioned MRS or DTT) are summarized as "easy to treat" (ETT) [15, 16].

The diagnosis of infection prior to the two-stage procedure was based on clinical signs, blood work (ESR, CRP), and positive synovial fluid aspiration and was confirmed by intraoperative cultures (following the state of the art [17, 18]). The two-stage revisions included removal of implants and bone cement (Stage I). All patients received a static antibiotic containing cement spacer as well as systemic antibiotics based on organism sensitivity for 2 weeks intravenously and for an additional 4 weeks orally. The knee spacers were performed as static, hand-made spacers with an endoskeleton [19]. Two weeks after stopping the systemic antibiotics successful eradication was confirmed by repeat joint aspiration. If the aspiration was negative, CRP was remained less than 2 g/dL and there was no sinus tract, a new implant was inserted (Stage II). After reimplantation, a 2-week i.v. antibiotic treatment and subsequent oralization were performed [20].

Reinfection (main outcome), following the recommendations of the International Consensus Group by the Musculoskeletal Infection Society [18], was diagnosed by clinical signs, blood work (ESR, CRP), and positive synovial aspiration. Patients with successful two-stage procedure (no major or minor criteria for infection during follow-up) served as controls. The minimum follow-up was 24 months.

Continuous variables are presented as mean ± SD (if normal distributed) (range, if no normal distribution occurred) and categorical variables are described as frequency (percentage). DTT, ETT and MRS were compared between patients who developed recurrence and those who had a successful outcome with univariate analysis using Chi square/Fisher's exact test.

Possible risk factors were analyzed. Patients' demographics, comorbidities, clinical and intraoperative findings and possible risk factors were compared between patients who developed recurrence and those who had a successful eradication/outcome also with univariate analysis using *t* test or Chi square test/Fisher's exact test. Additionally, the odds ratio of comorbidities, risk factors and clinical and intraoperative findings were calculated.

Logistic regression was performed to identify risk factors for reinfection. Model fitting for the logistic regression started with a full model including all risk factors that were significant in univariate analysis. The Hosmer–Lemeshow test of goodness-of-fit was performed and indicated that the logistic model fit the data well ($p = 0.853$). Statistical significance was set at $p < 0.05$. Post hoc power analyses were performed with use of observed proportions and sample sizes from Fisher's exact test. All statistical analyses were performed using IBM SPSS Statistics software version 23 (IBM Corp., Armonk, NY, USA).

Results

Recurrence of infection was diagnosed in 18 patients (18.8%) after two-stage reimplantation. All patients underwent additional surgical intervention: four patients were treated by irrigation and debridement (I&D), nine patients underwent a second two-stage procedure, in five patients an arthrodesis was necessitated; one patient, who underwent an arthrodesis, suffered from a persistent infection, so that a distal femoral amputation had to be done.

Study populations' demographics including univariate analysis are shown in Table 1. Age, gender, and BMI were similar in both groups (recurrence vs. eradication) (Table 1). Distribution of pathogens during two-stage procedure is shown in Fig. 1.

There were no significant differences of recurrence between each organism-group (DTT, ETT, MRS) (Table 2).

Table 1 Univariate analyses of patients' demographics

	Total (n = 96)	Recurrence (n = 18)	Eradication (n = 78)	p value
Sex				0.451
Male	52 (53.1%)	11 (11.5%)	40 (41.7%)	
Female	45 (46.9%)	7 (7.3%)	38 (39.6%)	
Side				0.433
Right	48 (50%)	7 (7.3%)	41 (42.7%)	
Left	48 (50%)	11 (11.5%)	37 (38.5%)	
Age (years)		66.5 (± 10.1)	70.7 (± 9.5)	0.102
BMI (kg/m^2)		26 (± 5.4)	31.2 (± 4.4)	0.327
ASA		2.88 (range 2–4)	2.8 (range 2–4)	0.636

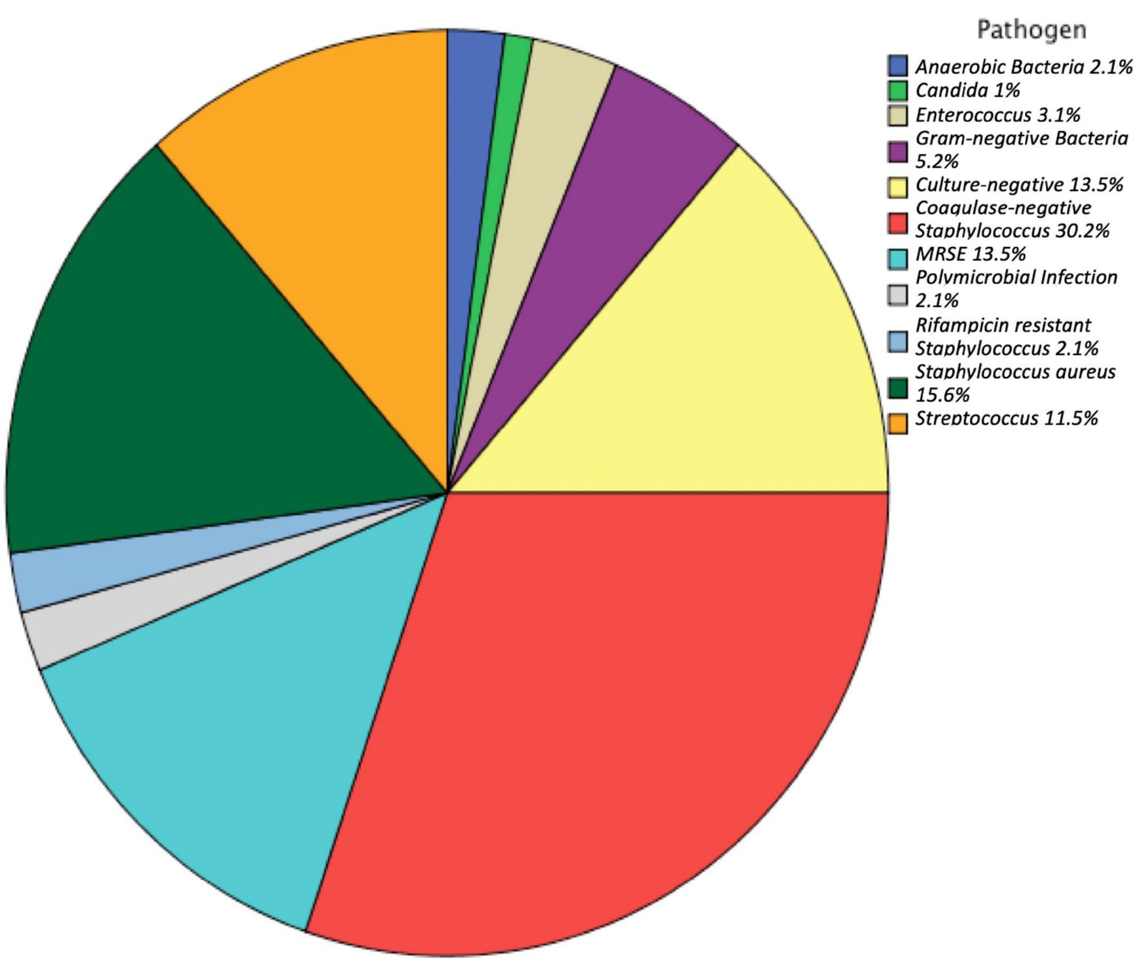

Fig. 1 Distribution of pathogens during two-stage procedure. ETT (80.2%): anaerobic bacteria, Gram-negative bacteria, culture-negative infection, coagulase-negative staphylococci, polymicrobial infection, *Staphylococci aureus*, streptococci; DTT (6.3%): candida, enterococci, rifampicin resistant staphylococci; MRS (13.5%): MRSE, MRSA

Table 2 Reinfection rates for each organism-group (easy to treat: ETT; difficult to treat: DTT; methicillin resistant staphylococci: MRS) and Fisher's exact test between organism-groups are shown

	Reinfection		Total	Fisher's exact test *p*-value	
	Yes	No			
ETT					
n	15	62	77	ETT vs DTT	0.674
%	19.5	80.5	80.2	ETT vs MRS	0.537
DTT					
n	1	5	6	DTT vs MRS	0.705
%	16.7	83.3	6.3		
MRS					
n	2	11	13		
%	15.4	84.6	13.5		

A statistical difference of eradication rates could not been shown

The results of the univariate analysis are shown in Tables 3 and 4. Four factors discover statistical significant differences (recurrence vs. eradicated): need of revision after first stage, need of revision after second stage, numbers of surgeries and alcohol abuse. In the group of ETT-patients the use of clindamycin-laden spacer shows a statistically significant difference too ($p=0.037$). No antibiotic (rifampicin, vancomycin, levofloxacin, clindamycin, flucloxacillin, linezolid, moxifloxacin) showed a significant difference in treatment success, except of moxifloxacin for MRS-patients (2 of 3 patients who were treated with moxifloxacin suffered from a reinfection, $p=0.038$).

The regression model increases the correct prediction of "recurrence of infection" (main outcome) from 81.3 to 88.5% after model fitting. Although four factors showed a significant difference in the univariate analysis, only two factors proofed significance in the logistic regression model: need of any revision after completed

Table 3 Univariate analyses of peri- and postoperative findings and treatments

	Total ($n=96$)	Recurrence ($n=18$)	Eradication ($n=78$)	Odds ratio	*p* value
Use of antibiotics prior to work up for periprosthetic joint infection				0.29	0.457
Yes	14 (14.6%)	13 (13.5%)	1 (1%)		
No	82 (85.4%)	65 (67.7%)	17 (17.7%)		
Pathogen in preop. synovial fluid				2.63	0.124
Yes	51 (65.4%)	45 (57.7%)	6 (7.7%)		
No	27 (34.6%)	20 (25.6%)	7 (9%)		
Fistula preoperative				1.53	0.692
Yes	12 (12.5%)	9 (9.4%)	3 (3.1%)		
No	84 (87.5%)	69 (71.9%)	15 (15.6%)		
Change of spacer				2.03	0.391
Yes	10 (10.4%)	7 (7.3%)	3 (3.1%)		
No	86 (89.6%)	71 (74%)	15 (15.6%)		
Use of antibiotic chain/beads				5	0.078
Yes	6 (6.3%)	3 (3.1%)	3 (3.1%)		
No	90 (93.8%)	75 (78.1%)	15 (15.6%)		
Clindamycin laden spacer				0.27	0.058
Yes	36 (37.9%)	33 (34.7%)	3 (3.2%)		**0.037** in ETT
No	59 (62.1%)	44 (46.3%)	15 (15.8%)		
Vancomycin laden spacer				0.71	0.771
Yes	26 (27.4%)	22 (23.2%)	4 (4.2%)		
No	69 (72.6%)	55 (57.9%)	14 (14.7%)		
Duration of inserted spacer in weeks		14.87 (±15.96)	14.56 (±5.96)		0.935
Numbers of surgeries		1.19 (±0.72)	1.67 (±1.14)		**0.028**
Revision needed after first step				5.62	**0.019**
Yes	10 (10.4%)	5 (5.2%)	5 (5.2%)		
No	86 (89.6%)	73 (76%)	13 (13.5%)		
Revision needed after completed two-stage protocol				29.07	**< 0.001**
Yes	15 (15.6%)	4 (4.2%)	11 (11.5%)		
No	81 (84.4%)	74 (77.1%)	7 (7.3%)		

Bold values indicate statistically significant results

Table 4 Univariate analyses of comorbidities

	Total ($n=96$)	Recurrence ($n=18$)	Eradication ($n=78$)	Odds ratio	p value
Diabetes mellitus				0.27	0.075
Yes	27 (28.1%)	25 (26%)	2 (2.1%)		
No	69 (71.9%)	53 (55.2%)	16 (16.7%)		
Arterial hypertension				0.46	0.257
Yes	83 (86.5%)	69 (71.9%)	14 (14.6%)		
No	13 (13.5%)	9 (9.4%)	4 (4.2%)		
Peripheral artery disease					1
Yes	4 (4.2%)	4 (4.2%)	0 (0%)		
No	92 (95.8%)	74 (77.1%)	18 (18.8%)		
Rheumatoid arthritis				0.86	1
Yes	6 (6.3%)	5 (5.2%)	1 (1%)		
No	90 (93.8%)	73 (76%)	17 (17.7%)		
Coronary heart disease				0.61	0.372
Yes	41 (42.7%)	35 (36.5%)	6 (6.3%)		
No	55 (57.3%)	43 (44.8%)	12 (12.5%)		
Chronic heart failure				0.55	0.278
Yes	43 (44.8%)	37 (38.5%)	6 (6.3%)		
No	53 (55.2%)	41 (42.7%)	12 (12.5%)		
Chronic kidney failure				0.65	0.452
Yes	34 (35.4%)	29 (30.2%)	5 (5.2%)		
No	62 (64.6%)	49 (51%)	13 (13.5%)		
Chronic obstructive pulmonary disease				0.36	0.454
Yes	12 (12.5%)	11 (11.5%)	1 (1%)		
No	84 (87.5%)	67 (69.8%)	17 (17.7%)		
Smoking				3.43	0.088
Yes	10 (10.4%)	6 (6.3%)	4 (4.2%)		
No	86 (89.6%)	72 (75%)	14 (14.6%)		
Alcohol abuse				5.62	**0.019**
Yes	10 (10.4%)	5 (5.2%)	5 (5.2%)		
No	86 (89.6%)	73 (76%)	13 (13.5%)		
Malignancies					0.118
Yes	11 (11.5%)	11 (11.5%)	0 (0%)		
No	85 (88.5%)	67 (69.8%)	18 (18.8%)		

Bold value indicates statistically significant results

two-stage revision (regression-coefficient 3.5, odds ratio 32.58, confidence interval 95% 6.4–165.7, $p<0.001$) and alcohol abuse (regression-coefficient 1.9, odds ratio 6.76, confidence interval 95% 1.12–40.7, $p=0.037$) turned out as a risk factor. The need of any revision in the interval of the two-stage procedure ($p=0.478$) and the numbers of surgery ($p=0.561$) showed no statistical significant effect in the regression model.

In the group of ETT the use of clindamycin in spacer cement showed a protective value (regression-coefficient −2.51, odds ratio 0.08, confidence interval 95% 0.008–0.87, $p=0.04$).

Discussion

The most important finding of the current study is that there are no pathogen-dependent differences in recurrence rates after two-stage procedure for periprosthetic knee infection. DTT organisms as well as MRS organisms show similar eradication rates to ETT organisms. Second, four risk factors could be shown: any revision needed after completed two-stage procedure (e.g. need of haematoma removal, wound dehiscence) is the main risk factor; revision needed in the interval between first and second stage (e.g. persistent infection, spacer complication) and numbers of surgeries go hand in hand and also represent a risk factor, although greater emphasis could not be shown with logistic regression analysis. At last, alcohol abuse also poses a risk for higher recurrence rates after two-stage exchange.

The finding that there is no organism-dependent difference in recurrence rate after two-stage protocol for periprosthetic knee infection is still debatable in the current literature. Akgun et al. [15] are in line with our numbers (success rate between 80 and 84%) and reported about no difference between DTT and non-DTT. However, another study from the same institute [21] reported a significantly higher recurrence risk for DTT compared to non-DTT bacteria (odds ratio = 4.8; 95% confidence interval = 1.4–16.4; $p = 0.02$). All studies [15, 21–23] (including the above-mentioned) have one thing in common: too small numbers of cases to achieve adequate power analyses and definitive conclusions.

From a microbiology view periprosthetic MRSA and MRSE infection are not classified as "difficult to treat". Some studies [24, 25] showed cure rates from up to 91% (levofloxacin in combination with rifampicin) in an animal model. In contrast, periprosthetic infection with fluorquinolone-resistant Gram-negative bacteria, rifampicin-resistant Staphylococci, Enterococci, and Fungi are classified as "difficult to treat". Corvec et al. [26] described a highest cure rate for fluorquinolone-resistant Gram -negative bacteria with 67% (fosfomycin in a combination with colistin). Other studies [27, 28] showed a highest cure rate for Enterococci with 58% (gentamycin and fosfomycin in a combination treatment), also in an animal model. Winkler et al. [12] referred to the difficult treatment of Fungi and rifampicin-resistant Staphylococci. In spite of this literature we could not find a difference in the recurrence rate between DTT and ETT group. By the similar recurrence rate we think that the stratification of organisms is useful, but should not be overstated. It should be noted that the bacterium-specific antibiotics is a prerequisite of successful therapy. The different, organism-depending cure rates in the animal models and in clinical studies suggest that other factors in the context of a two-stage exchange play a significant role. Next to the stratification of the organisms, other risk factors have occurred. The number of surgeries and the need of a revision during or after a two-stage protocol seem to play an important role. This fact underlines the importance of a thorough debridement and conscientious placement of the spacer at the first-stage surgery.

The overall eradication rate in our study population was 81.3%. This number is in line with other current studies (Ma et al. [29] success rate of 84%, Hipfl et al. [21] 84%, Akgun et al. [15] 82.8%, respectively). Low inferior data from a tertiary center were reported by Schwarzkopf et al. [30]: a two-stage reimplantation and infection eradication could be achieved in 64%. A two-stage reimplantation alone could be achieved in 70.7%.

On the other hand, microbiological eradication studies [24, 25, 27, 28, 31–33] show a maximum eradication rate of 67% in DTT-infections and a maximum eradication rate of 91% in MRS-infections. These numbers are not consistent with overall eradication rate in the current study of 81.3%. These findings reflect the multiple factors of a successful two-stage procedure.

The current study has a number of limitations. First of all, only 6 DTT patients and 13 MRS patients are analyzed. Further studies with more cases of DTT and MRS infections are necessary to emphasize the current findings. Although Fisher's exact test is a good possibility to get valid statistical statements with smaller numbers of cases [34]. The current study already includes, next to two other studies [15, 23], the largest numbers of patients, although the numbers of cases led to a slightly underpowered study [34].

Second, although we made sure that we treated each patient with the exact equal two-stage protocol, every single PJI case is unique with not yet understood variables: every single resistogram is different, followed by a patient (comorbidities, in particular lever and kidney function) and organism dependent antibiotic-treatment. The number of cases is too small to analyze groups of different resistograms. Finally, as a tertiary referral center the exact medical history, in particular the use and duration of antibiotics, sometimes the numbers and types of prior surgeries, is difficult to validate; therefore, the included patients may be biased, this circumstance may be influence the overall eradication rate as well.

Conclusion

In summary, we could not find a difference between organism-groups (ETT, DTT and MRS) in recurrence rates after two-stage protocol for periprosthetic knee infection. Although in animal models cure rates for DTT organisms of 58–67% are described, the current study can show a recurrence free percentage of 83.3%. Therefore, the individualization of therapy regimes with improved outcomes no longer permits the use of the nomenclature of "difficult-to-treat".

Author contributions FM: planning/conception of the study, collection of data, analysis and interpretation, statistical analysis, writing and revising article; (orthopedic surgeon). WC: collection of data, analysis and interpretation, statistical analysis; (student). BR, KT, FT: collection of data, critical revision of the article; (orthopedic surgeons). RH: critical revision of the article, final approval of the article, overall responsibility; (surgeon in chief University of Ulm).

Compliance with ethical standards

Conflict of interest We certify that we have not signed any agreement with commercial interest related to this study, which would in any way limit publication of any and all data generated for the study or to delay publication for any reason. Dr. Faschingbauer reports personal fees from Deutsche Forschungsgemeinschaft (Research Fellowship, FA 1271/1-1, http://www.dfg.de), during the conduct of the study.

Ethical statement The authors' institutional review board approved this study.

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