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Do not exchange the spacer during staged TKA exchange!

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ABSTRACT

Purpose: The aim of this study was to investigate the reinfection rate and risk factors for septic failure after two-stage exchange for chronic periprosthetic joint infections of primary total knee arthroplasties. Reinfections should be classified as new infection or as infection recurrence after two-stage exchange.
Methods: We performed a retrospective study of 60 knees with chronic periprosthetic joint infections. Follow-up information was extracted from the departments electronic database.
Results: The reinfection rate after a mean follow-up of 35.6 months (1–135) was 20.0%. The only significant risk factor for reinfection was spacer exchange during two-stage exchange (OR = 10.42; p = 0.001). Of the 12 cases with reinfection 6 cases were classified as new infection and 2 as infection recurrence.
Conclusions: Patient specific factors for reinfection remain furtive. If a spacer exchange is preformed, the risk of reinfection increases. Culture results indicate that the benefit of spacer exchanges during two-stage exchange is highly questionable, particularly because reinfection is an issue of new infection rather than of infection recurrence.

1. Introduction

Periprosthetic joint infections (PJI) are a devastating complication after Total Knee Arthroplasty (TKA). The risk of PJI after primary TKA is reported to be as low as 0.5%–1.9%,[1] nonetheless between 14.8% and 25.0% of TKA revisions are performed because of PJI.[2–5] The absolute number of PJIs after TKA should rise because of the expected increase of primary TKA.[6] The gold standard for the treatment of PJI is the two-stage exchange (TSE).[1,7,8] Latest reviews report the range for reinfection rates after TSE at the knee between 0% and 41%.[9]

If reinfection after TSE occurs, the discrimination between infection recurrence with the same pathogen and new infection with a different pathogen may take decisive influence on further treatment strategies.[10] The review by Jamsen et al. describes an infection recurrence rate of 0–18% and a new infection rate of 0–31%, respectively.[11] An evident explanation for the broad range of reinfection rates is lacking.

So far, particularly previous revisions anteceding TSE have been shown to increase the risk of reinfection.[11–13] However, septic failure rates in multicenter studies have been reported to be beyond 20.0%, even when cases with previous revisions anteceding TSE were excluded. For these studies, the heterogeneity in PJI definitions and treatment modalities remain a serious limitation.[14] In general, TSE comprises at least two operations. At the first stage, the infected TKA is removed to implant an antibiotic loaded interim spacer. At the second stage, the spacer is removed and a new TKA implanted. In between these two stages, spacer exchange to place a second antibiotic load in to the affected joint is a treatment option for persisting infection. Although accepted in clinical practice,[15] the indication for as well as the advantages and disadvantages of a spacer exchange have only been mentioned in few studies.[12] Thus, the need for discrimination of TSE with and without spacer exchange has not been emphasized within the scientific body. Additionally, the impact of spacer exchange on reinfection after staged TKA exchange is unknown.

The aim of this study was to investigate the reinfection rate of TSE with articulating spacers for chronic PJI after primary, bicondylar resurfacing TKAs. Factors that influence the risk of failure after TSE were analyzed. By comparing pathogens detected at PJI diagnosis to those detected at septic failure after TSE reinfection was classified as new infection or as infection recurrence.

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2. Methods

2.1. Patient inclusion

Ethics approval was waived by the institutional Ethics Commission for this retrospective observational study. All TKA removals with spacer implantation performed at the study institution between 2008 and 2016 were retrospectively identified (N = 274). Patients with previous revisions (N = 162), patients with a TKA of a constraint level higher than posterior stabilized (N = 12), patients that received a static spacer at TKA removal (N = 2), and patients without reimplantation (N = 3) were excluded. Further 27 that did not fulfill the PJI definition according to the Infectious Disease Society of America (IDSA) and 3 patients, who received a distal femur replacement or an arthrodesis at reimplantation were excluded. Finally, 4 cases without follow-up information and one patient with acute PJI defined by symptoms of less than 3 weeks were excluded.[7,15,16] Therefore, the study population comprised 60 patients that had undergone TSE for a chronic PJI of a primary, unrevised TKA with a bicondylar surface replacement.

2.2. Treatment protocol TSE

At stage one the prosthesis was removed, infectious altered tissue and bone was debrided and an articulating spacer implanted. The spacer was molded by hand from a 0.5 g gentamicin premixed polymethylmethacrylat bone cement additionally blended with 2 g of vancomycin per 40 cc batch of cement. If preoperative cultures from aspiration yielded no growth, the antibiotic therapy was started with a combination of an aminoglycoside and a cephalosporin. In case of bacteria growth from intraoperative tissue samples antibiotic therapy was adapted according to the infectiologist's recommendation. Antibiotic therapy was administered for 2 weeks intravenously. During this period, the CRP and wound healing was monitored for signs of ongoing infection. Intravenous antibiotic therapy was followed by 4 weeks of oral administration on an outpatient basis. At the time of patient inclusion TSE was performed with joint aspiration before reimplantation. Therefore, two weeks after antibiotic therapy cessation the joint was aspirated and a synovia sample cultured for 16 days. Presence of infection before planned reimplantation was considered, if these cultures yielded a pathogen, if the course of the C-reactive protein (CRP) was not adequately decreasing in conjunction with local signs of infection, such as erythema, fistula, wound healing problems and/or purulence around the spacer. If infection persisted until planned reimplantation, the spacer was exchanged and second course of antibiotic therapy started. Otherwise TSE was continued with reimplantation.

2.3. Patient characteristics

39 patients (65.0%) were female patients. TSE was initiated 53.5 months (2–239) after primary TKA. 43 patients (71.7%) were referred to our institution. Mean age was 67.8 years (46–85), mean BMI 31.7 kg/m^2 (18.3–65.2) and mean American Society of Anesthesiologists (ASA) score 2.6.[2–4] 53 TKAs (88.3%) were performed because of idiopathic osteoarthritis, 5 (8.3%) because of posttraumatic osteoarthritis and 2 (3.3%) because of a rheumatic etiology. Reimplantation was done with a condylar constrained prosthesis in 10 (16.7%) patients and the remaining patients with a rotating hinge prosthesis.

2.4. Risk factors for reinfection

The following potential risk factors were collected from the patients records: Demographic data (BMI, age, sex, ASA score, smoking habit, Diabetes mellitus, chronic anticoagulant use, duration from primary TKA to TSE) and variables at prosthesis removal as well as at reimplantation (pathogen detected from aspirated synovial fluid cultures and intraoperative tissue samples, purulence around prosthesis, loosening of the prosthesis, appearance of a sinus tract, operation time at removal, Glomerular Filtration Rate (GFR), blood sugar level and CRP. TSE variables (spacer exchanges during TSE) were also extracted.

2.5. Follow-up and reinfection

Follow-up information was extracted from the electronical records at last contact with our department. Reinfection was defined as the need for revision surgery due to PJI also defined according to IDSA guidelines or the need for suppressive antibiotic therapy at last follow-up. Reinfection after TSE was classified as infection recurrence and new infection. Infection recurrence was defined as reinfection with the same pathogen. New infection was defined as reinfection with another pathogen than detected at PJI diagnosis.[10]

2.6. Statistical analysis

To assess significances between groups, patients were grouped into two different subgroups according to their infection status: reinfection free patients and patients with reinfection. Potential metric risk factors between groups were analyzed with the Mann-Whitney-U test. Potential, nominal risk factors are depicted as Odds ratio (OR) and were tested for significance with the Pearson's Chi -Square test. Survival was calculated with Kaplan-Meier-analysis. Cumulative survival between groups was compared with the log-rank-test.

P-values of less than 0.05 were considered statistically significant. All statistical analyses were calculated using SPSS Vers. 24 (Chicago, IL, USA).

3. Results

3.1. Reinfection rate

The reinfection rate after a mean follow-up of 35.6 months (1–135) was 20.0% (N = 12). Of these 12 patients with septic failure after first TSE, 2 patients were successfully treated with debridement, antibiotics, irrigation and implant retention and 3 patients with a second TSE. One patient had to be treated with above knee amputation because of soft tissue complications two months after the first TSE. 2 patients were amputated after failed, second TSE. One patient was successfully treated for reinfection with a second TSE but then suffered from aseptic loosening. Finally, one patient was managed with arthrodesis at stage two during the second TSE.

3.2. Risk factors for reinfection

Spacer exchange was the only significant risk factor (OR = 10.42; p

Table 1
Odds Ratio, p values and distribution of potential risk factors for reinfection.

Potential Risk Factor	OR (CI 95%)	p	% in group without reinfection (N = 48)	% in group reinfection (N = 12)
Spacer exchange	10.42 (2.08–55.56)	0.001	6.3	41.7
Sinus tract at diagnosis	4.61 (0.58–37.04)	0.121	4.2	16.7
Pathogen detection at removal	3.55 (0.85–14.71)	0.071	45.8	75.0
ASA score >2	3.26 (0.9–13.559	0.093	47.9	75.0
Elevated CRP at diagnosis	3.00	0.171	62.5	83.3

OR: Odds Ratio; ASA: American Society of Anesthesiologists; CRP: C-reactive Protein.

= 0.001) for reinfection. Potential risk factors with OR ≥ 3 are depicted in Table 1. We found no significant differences for any other collected patient characteristic variables, which are listed under the subheading "risk factors" in the methods section.

Fig. 1 displays the cumulative estimated infection free survival for patients treated with and without spacer exchange. Log-rank test showed significant better infection free survival in patients that did not undergo spacer exchange during TSE (p = 0.002).

Of the 60 included TSEs, 52 were conducted without and 8 were conducted with spacer exchange. The reinfection rate in the group of patients with spacer exchange was 62.5% (5/8) but in the group without spacer exchange 13.5% (7/52) but in the group. Fig. 2 illustrates the correlation of spacer exchange to reinfection.

4. Discussion

This study analyzes the outcome of 60 patients suffering from chronic PJI at the knee treated with TSE with articulating spacers. For TSE without the need of spacer exchange we found a reinfection rate of 13.5%, which is in range of the reported literature. However, in the literature this range spreads from 0% to 41%.[9,11] Although evidence is lacking, we believe that patient factors, treatment modalities concerning local and systemic antibiotic therapy and different philosophies concerning the principles of conducting TSE influence the outcome. In the presented study, spacer exchange was the only significant indicator for septic failure after reimplantation with an OR of 10.42 – or in other words, 62.5% of patients that had the spacer exchanged failed after reimplantation because of reinfection (Fig. 2).

Whether a spacer exchange is the reason for reinfection or reinfection is the consequence of insufficient infection eradication despite re-debridement with placement of a second antibiotic load into the knee by spacer exchange is essentially a chicken and egg problem. In Fig. 3 we address this problem on the basis of intraoperative pathogen detection in the 8 patients that had a spacer exchanged.

The presented pathogen detections can be interpreted as follows: First, the 2 cases with pathogen detection at reimplantation were infected during spacer exchange. Indications for spacer exchange were inadequate CRP decrease in one and spacer dislocation in the other patient. Second, the 4 cases with no pathogen detection at reimplantation were unnecessarily spacer exchanged. Indications in these cases were inadequate CRP decrease in two cases, purulence around the spacer in one case and finally remaining foreign material from the first stage. And third, only the two cases with pathogen detection at spacer exchange but no pathogen at reimplantation benefited from spacer exchange. In these cases, indication for spacer exchange were inadequate CRP decrease, too. However, they suffered from new infections after reimplantation anyway. In summary, 6 of 8 patients did not benefit from spacer exchange.

Indications for spacer exchange are not defined and by far not consented. Particularly joint aspiration with indwelling spacer has demonstrated useless sensitivities for routine detection of persistent infection,[17,18] which is why it was abandoned at the study institution. The role of CRP testing is controversially discussed. While some authors report significantly higher values in case of infection persistence others have reported even significantly lower values.[19,20] Thus, based on the available means for evaluating infection persistence during TSE we query the usefulness and sensibility of spacer exchanges. This conclusion is underlined by the fact, that reinfection after TSE is predominantly caused by new infection and not by infection recurrence.

There are limitations to the current study. Significant risk factors for reinfection after TSE might not have been identified because of a type II error. Because of the retrospective design follow-up was short in some patients, meaning that 9 of the 60 included patients had a follow-up of less than one year. However, series sizes and follow-up periods in the literature are highly variable[9,11] and only very few studies have excluded previous TSEs or TKA revisions: Watts et al. published a series of 111 first TSEs with a mean follow-up of 5.1 years in 2014. This study reports a significantly higher reinfection rate for morbidly obese patients of 22%. However, previous aseptic revisions, that have also been shown to increase the risk of reinfection,[11–13] were not excluded. Cochran et al. analyzed 5364 PJIs after primary TKA from the Medicare Data base treated with TSE. The reinfection rate after one year was 19% and 29.1% after six years, but further investigation on risk factors for reinfections were not conducted.[14] In contrast to the cited, the current study is outstanding because of its' strict inclusion criteria with only chronic PJIs after primary resurfacing TKAs and because of the homogenous treatment modalities from one single department.

Conclusions on the effect of spacer exchange and classification of reinfection are based on tissue sampling from a joint with an indwelling antibiotic loaded spacer. Bacteria shifts of about 75% between the stages of TSE have been reported before.[20,21] However, a definite explanation is missing. Antibiotics released from the spacer and accumulated in the sampled tissue may hamper culturing or may give an advantage in growth for less susceptible bacteria. The change of identified bacteria during and after TSE may also be owed to polymicrobial infection with altering pathogen domination. Thus, the objection, that the change of

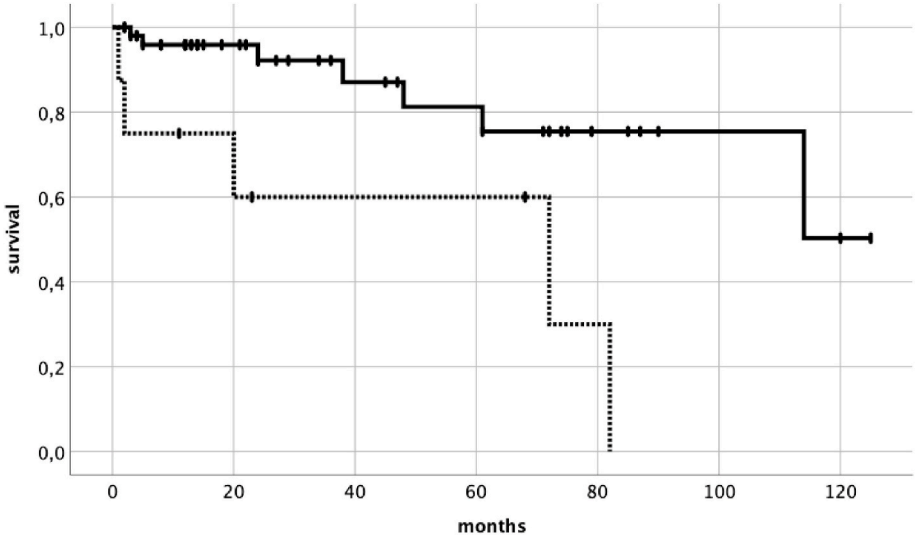

Fig. 1. Kaplan-Meier-Curve demonstrating reinfection free survival grouped by spacer exchange and no spacer exchange during TSE.
Continuous line: patients without spacer exchange during TSE, dotted line: patients with at least one spacer exchange during staged TKA exchange.

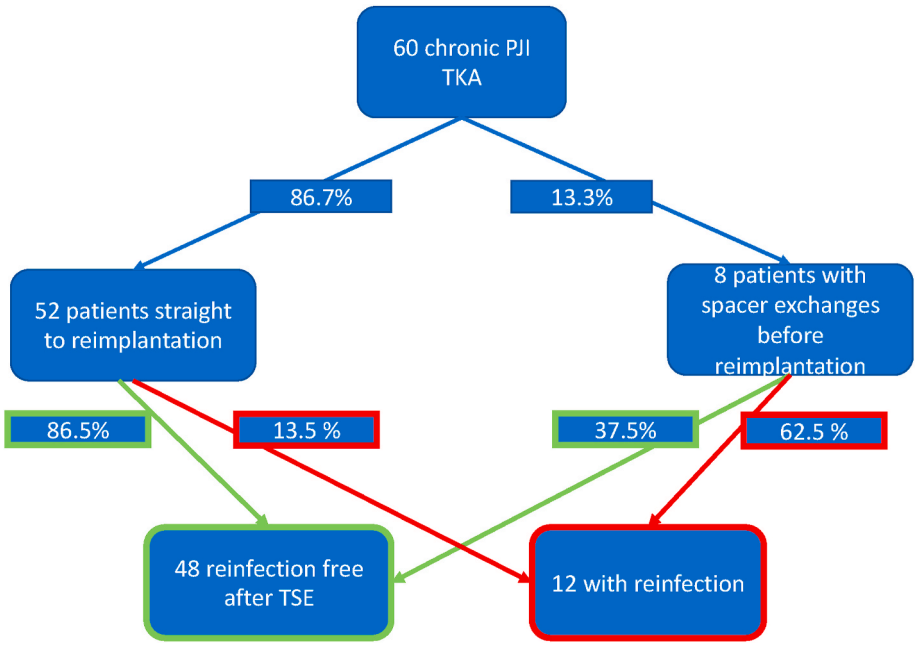

Fig. 2. Illustration of reinfections for patients with and without a spacer exchange.
Reinfection classification Of the 12 cases with reinfection 6 cases were classified as new infection and 2 as infection recurrence. Details are shown in Table 2.

Table 2
Reinfections classified as infection recurrence and reinfection.

Classification of reinfection	Pathogen at PJI diagnosis	Pathogen at reimplantation	Pathogen at reinfection
New infection	St. epidermidis	None	Micrococcus luteus
New infection	*Enterococcus faecalis*	*Enterobacter cloacae*	*Enterobacter cloacae*
New infection	St. aureus	Candida parapsilosis	Candida parapsilosis
New infection	alpha-haemolytic Streptococci	None	MRSA
New infection	MRSA	None	St. aureus
New infection	Pseudomonas	None	St. epidermidis
Infection recurrence	St. aureus	None	St. aureus
Infection recurrence	St. aureus	None	St. aureus
Unclear	St. epidermidis	None	None
Unclear	None	None	St. epidermidis
Unclear	None	None	Streptococcus agalactiae
Unclear	St. capitis	None	None

St.: Staphylococcus; MRSA: Multiresistant St. aureus.

detected bacteria types are the result of incontrollable infection is warranted. However, since tissue culturing still is the gold standard for pathogen detection and detected pathogens are decisive for PJI treatment, these results have to be discussed and must not be disregarded.

5. Conclusion

Patient specific factors for reinfection remain furtive. If a spacer exchange is preformed, the risk of reinfection increases. Culture results indicate that the benefit of spacer exchanges during the TSE is highly questionable, particularly because reinfection is by far more an issue of new infection than of infection recurrence. If persistent infection during TSE is assumed we recommend to perform the removal of the spacer and reimplantation as a one-stage exchange.

Ethical approval

This study is a retrospective, observational study evaluating a standard treatment regime at our institution. No additional interventions were performed. No additional data were gathered for this study. Ethics approval was waived by the Ethics Commission of the Medical Faculty of the University of Wuerzburg, Germany (Reference number 2016072801).

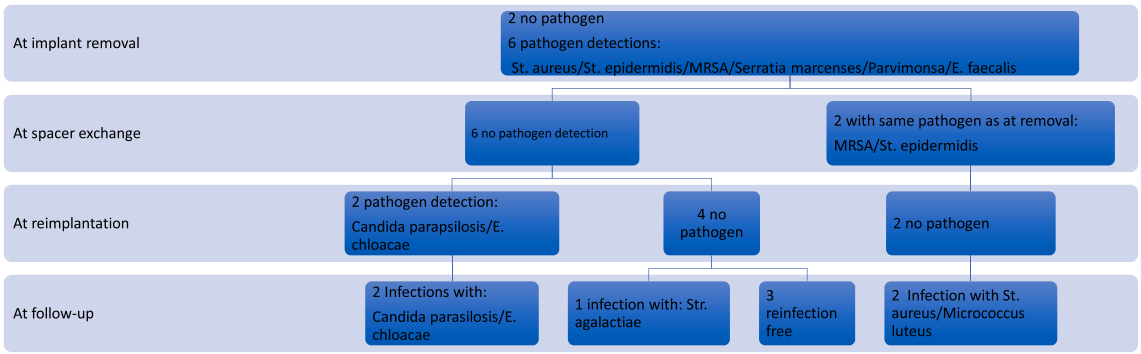

Fig. 3. Pathogen detection from the 8 patients with spacer exchange during TSE and at follow-up.

Consent for publication

All presented data are anonymized. Consent for publication was waived by Ethics Commission of the Medical Faculty of the University of Wuerzburg, Germany.

Availability of supporting data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SB and ML did the conceptualization. SB, PH and AJ collected the data. SB, AJ and MR wrote the manuscript. JA, YK and ML drafted and reviewed the manuscript. MR supervised the study. All authors approved the final manuscript.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

PJI	Periprosthetic Joint Infection
TKA	Total Knee Arthroplasty
TSE	Two-stage exchange
IDSA	Infectious Disease Society of America
CRP	C-reactive protein
ASA	American Society of Anesthesiologists
GFR	Glomerular Filtration Rate
OR	Odds Ratio

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