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ORIGINAL PAPER

# Polymicrobial infections reduce the cure rate in prosthetic joint infections: outcome analysis with two-stage exchange and follow-up ≥two years

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**Abstract**
*Purpose* Prosthetic joint infections (PJI) are a serious and challenging complication after total joint arthroplasty. According to the literature, most PJI are monomicrobial infections caused by gram-positive cocci. The number of polymicrobial PJI might be underrepresented in the literature and only limited data are available regarding the outcome of polymicrobial PJI. Our hypothesis was that polymicrobial PJI are associated with a reduced cure rate compared with monomicrobial PJI.
*Methods* Routine clinical data were collected and analysed retrospectively as anonymised, aggregated data. A total of 77 consecutive patients with 77 confirmed PJI and proven infectious organism of the hip and knee joint treated within a two-stage exchange concept and a follow-up ≥ two years were investigated. Detection of the infectious organism was based on multiple microbiological cultures taken intra-operatively. Superficial wound swabs or swabs from sinus tracts were not taken into account. Data were grouped into polymicrobial and monomicrobial PJI. The main outcome variable was "definitively free of infection after two years" as published. Second, we considered several variables as potential confounders or as risk factors.
*Results* A total of 42 men and 35 women with 46 infected total hip arthroplasties and 31 infected total knee arthroplasties were evaluated. In 37 (46.6 %) of our 77 patients a polymicrobial PJI could be detected. We found a significant association between polymicrobial PJI and the outcome parameter definitively free of infection after two years with an odds ratio (OR) of 0.3 [95 % confidence interval (CI) 0.1–1.0]. The rate of patients graded as definitively free of infection after two years was 67.6 % for polymicrobial infections vs. 87.5 % for monomicrobial infections. The American Society of Anesthesiologists (ASA) score (OR 0.4, 95 % CI 0.2–1.0, $p$=0.062) was identified as a borderline significant covariable.
*Conclusions* Our data suggest that polymicrobial PJI might be underrepresented in the current literature. Additionally, the presence of multiple infectious organisms is associated with a reduced rate after two years with 67.6 vs 87.5 % for monomicrobial infections. Special attention and extra care should be considered for these patients.

**Keywords** Infection · Revision · Polymicrobial · Arthroplasty · Prosthetic joint infection

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## Introduction

In accordance with the increasing absolute number of primary total joint arthroplasties (TJA), the frequency of revision surgery is increasing as well [1]. While aseptic loosening accounts for the majority of revision surgery, treatment and management of prosthetic joint infections (PJI) remains challenging with a potentially devastating outcome for our patients. In the literature PJI occur with an incidence of 1–3 % after primary TJA, but in cases of revision surgery the incidence increases to 12 % [2, 3]. Subsequently, PJI can be considered to

be one of the most often, most severe and most difficult to manage complications after TJA, and especially after revision TJA [4, 5].

The literature available on PJI reports mainly on monomicrobial infections when only one causative pathogen can be detected. Coagulase-negative staphylococci (30–43 %) and staphylococcus aureus species with 12–23 % have been determined to account for the majority of the cases [6, 7]. Polymicrobial infections have been consistently reported as worse or worst-case scenarios, but have been investigated in a relatively low number of publications. The few data available suggest a rate of polymicrobial infections ranging from 19 to 37 %, but mostly fail to quantify outcome in relation to monomicrobial infection and other risk factors [8, 9].

Recent publications do not recommend a distinct treatment algorithm for polymicrobial PJI [10–13]. Jackson and Schmalzried concluded that a one-stage exchange should not be performed in such cases [14]. Within a two-stage exchange concept, success rates regarding infect resolution in patients with polymicrobial PJI vary between 71.4 and 77.7 % [9, 15].

Additionally, up to now only a very few risk factors have been identified that affect the outcome of treating patients with polymicrobial PJI. To the best of our knowledge, Marculescu and Cantey published the only paper reporting on independent variables affecting the outcome after polymicrobial PJI [9]. They were able to identify soft tissue defects, wound dehiscence, drainage and age ≥ 65 years as independent variables.

Following this rationale and considering the lack of evidence, we investigated whether the presence of polymicrobial infections affects surgical outcome regarding the rate of patients graded as definitively free of infection with a minimum follow-up of two years [16]. This was done in patients with confirmed polymicrobial PJI of total hip arthroplasty (THA) or total knee arthroplasty (TKA) treated with a two-stage exchange concept.

Our primary hypothesis was that polymicrobial infections reduce the rate of resolution of infection. Our null hypothesis was that polymicrobial infections do not influence the outcome investigated. As potential confounders we included age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) score, THA vs. TKA, duration of infection, local extremity grade (McPherson 1–3) and systemic host grade (McPherson A–C) [17].

## Methods

Between November 2006 and November 2009, 77 consecutive patients were treated for chronic PJI of infected THA or TKA. All patients had confirmed PJI and at least one proven infectious organism and were treated with a two-stage exchange concept; no single-stage exchanges were performed. The minimum follow-up was two years [18].

### Patients

A total of 77 patients, 42 males and 35 females, were included. 46 (59.7 %) patients received revision of a THA, 31 (40.3 %) of a TKA. These patients were followed for 77±29.4 months on average. In 26 patients after THA (43.5 %) a polymicrobial infection was proven. In 11 patients with infected TKA (35.5 %) a polymicrobial infection was proven. Table 1 summarises the distribution of the infectious organisms detected. Both groups, patients with polymicrobial infection or without polymicrobial infection, did not vary significantly according to age, sex, weight, height and BMI. Table 2 shows basic demographics.

The treatment was based on the algorithm published by Zimmerli et al. [6, 19]. Patients were retrospectively allocated into two groups: patients with polymicrobial PJI (study group) and patients without polymicrobial PJI (control group). No patients were excluded because of systemic or local risk factors, previous infections and prior operations or presenting in a septic condition.

Routine clinical data were collected and analysed retrospectively and as aggregated data only. A PJI was considered proven if at least one of the following criteria was fulfilled (modified according to Laffer et al. [16]):

1. Purulent synovial fluid or≥1,700 leukocytes/μl or≥65 % neutrophils in the joint aspirate [20]
2. Histological confirmation of an acute inflammatory reaction with≥five neutrophils/"high-power field" in five representative areas [21, 22]

**Table 1** Distribution of infectious organisms detected in the patients treated

| | Polymicrobial PJI [37 (48.1 %)] | Monomicrobial PJI[40 (51.9 %)] |
|---|---|---|
| One infectious organism, *n* | | 40 |
| Two infectious organisms, *n* (%) | 17 (45.9) | |
| Three infectious organisms, *n* (%) | 16 (43.2) | |
| Four infectious organisms, *n* (%) | 4 (10.8) | |
| MSSA, *n* (%) | 17 (45.9) | 10 (25) |
| MRSA, *n* (%) | 10 (27) | 2 (5) |
| MSSE, *n* (%) | 29 (78.4) | 10 (25) |
| MRSE, *n* (%) | 16 (43.2) | 9 (22.5) |
| Streptococci, *n* (%) | 6 (16.2) | 4 (10) |
| Enterococci, *n* (%) | 11 (29.7) | 3 (7.5) |
| Gram-negative bacilli, *n* (%) | 8 (21.6) | 2 (5) |
| Fungi, *n* (%) | 1 (2.7) | 0 (0) |

*PJI* prosthetic joint infections, *MSSA* methicillin-susceptible staphylococcus aureus, *MRSA* methicillin-resistant staphylococcus aureus, *MSSE* methicillin-susceptible staphylococcus epidermidis, *MRSE* methicillin-resistant staphylococcus epidermidis

**Table 2** Demographic data and results of univariate analysis

| Variable | Polymicrobial PJI [37 (48.1 %)] | Monomicrobial PJI [40 (51.9 %)] | *p* value |
|---|---|---|---|
| Age at surgery (years) | 67.9 | 68.8 | 0.8919 |
| Sex, M/F (% male) | 16/21 (43.3) | 26/14 (65) | 0.0564 |
| Weight (kg) | 75.22 | 75.03 | 0.9795 |
| Height (m) | 1.66 | 1.68 | 0.7628 |
| BMI (kg/m$^2$) | 27.40 | 26.71 | 0.2942 |
| Hips, *n* (%) | 26 (70.3) | 20 (50) | 0.0695 |
| Knees, *n* (%) | 11 (29.7) | 20 (50) | 0.0695 |
| Side [*n*=right (%)/*n*=left (%)] | 24 (64.9)/13 (35.1) | 21 (52.5)/19 (47.5) | 0.2700 |
| Mean follow-up (months) | 28.38 | 30.43 | 0.7628 |
| ASA (mean) | 2.51 | 2.53 | 0.9976 |
| Duration of PJI until treatment (days) | 127.86 | 77.15 | <0.001 |
| McPherson 1 (local RF) | 4 (10.8 %) | 17 (42.5 %) | 0.0017 |
| McPherson 2 (local RF) | 16 (43.2 %) | 13 (32.5 %) | 0.3186 |
| McPherson 3 (local RF) | 17 (45.9 %) | 10 (25 %) | 0.0537 |
| McPherson A (systemic RF) | 3 (8.1 %) | 8 (20 %) | 0.1321 |
| McPherson B (systemic RF) | 11 (29.7 %) | 16 (40 %) | 0.3586 |
| McPherson C (systemic RF) | 23 (62.2 %) | 16 (40 %) | 0.0537 |
| No. of revisions external (mean) | 2.46 | 1.23 | 0.8314 |
| No. of revisions internal (mean) | 5.43 | 2.23 | 0.6295 |
| Adequate external therapy | 17 (45.9 %) | 24 (60 %) | 0.2186 |

*PJI* prosthetic joint infections, *BMI* body mass index, *ASA* score of the American Society of Anesthesiologists, *RF* risk factors

3. Pathogen detection in sterile joint aspiration or in at least two intraoperative tissue specimens after incubation
4. Definite signs of PJI clinically or intraoperatively (e.g. sinus tract) [6]

A polymicrobial infection was considered proven according to Steckelberg and Osmon [23]:

1. Two or more identical infectious organisms detected by joint aspiration and at least one intraoperative tissue sample
2. Two or more identical infectious organisms detected by at least two intraoperative tissue samples
3. Two or more identical infectious organisms detected by at least one intraoperative tissue sample and a clinically evident PJI (i.e. sinus tract communication with the joint space, purulence in the joint, acute inflammation)

## Two-stage exchange

In brief, and as published elsewhere, the two-stage exchange concept surgery consisted of the removal of the infected prosthesis and extensive surgical debridement and irrigation [18]. Intravenous antibiotics were administered for at least 14 days, followed by oral therapy for four weeks. This interval was followed by a treatment window of two weeks without any antibiotic therapy, and then aspiration of the joint was performed for microbiological examination. If no infectious organism was detected and if labs did not reveal a residual infected situation, i.e. C-reactive protein (CRP)<10 mg/dl and WBC<10.2 G/l, a new prosthesis was reimplanted. If a pathogen was detected surgical debridement was performed prior to reimplantation. Antibiotic therapy was chosen according to the causative pathogen detected prior to the operation and administered postoperatively for six weeks (14 days i.v., 4 weeks p.o.). In cases of pathogen detection from samples acquired during reimplantation, debridement and retention of the prosthesis was performed. This was followed by three to six months of antibiotic therapy.

## Antibiotic therapy

The suitable antibiotic therapy was chosen in an interdisciplinary approach respecting the detected infectious organism, its susceptibility pattern and published recommendations [6, 19]. Frequent case discussions and rounds by both orthopaedic surgeons and clinical microbiologists guaranteed optimised treatment for our patients. Laboratory parameters for infection (CRP, WBC) as well as kidney and liver function were monitored constantly. Drug levels (i.e. vancomycin or gentamicin

levels) were routinely controlled and the dose administered was adapted accordingly.

### Outcome evaluation

To evaluate our hypotheses the success rate of our treatment was classified according to Laffer et al. as published [16]:

- "*Definitively free of infection*": no signs of infection, CRP≤10 mg/dl, follow-up≥two years
- "*Clinical resolution of infection*": no clinical signs of infection, follow-up≥two years
- "*Laboratory resolution of infection*": CRP≥10 mg/dl, follow-up≥two years
- "*Treatment failure*": persistence or recurrence of PJI with the same or an unknown pathogen during or after the completion of antimicrobial therapy

Additionally, we investigated whether patients with polymicrobial infections required more revision surgeries.

### Potentially confounding parameters

As potentially confounding parameters for polymicrobial infections we investigated the following items: age, gender, BMI, the ASA score, type of infected arthroplasty (THA vs TKA), recurrent PJI, duration of infection, local extremity grade (McPherson 1–3) and systemic host grade (McPherson A–C) [17].

An inadequate antibiotic therapy was defined as an antibiotic therapy (intravenous or oral) against published guidelines. This includes an empiric antibiotic therapy without respect to a proven infectious organism, inadequate duration of the antibiotic therapy or no oral bactericidal oral therapy, even though available.

An inadequate surgical therapy included all insufficient debridements against published guidelines, i.e. superficial soft tissue debridement only, debridement without exchange of mobile implant components or arthroscopic debridement. If a debridement or retention strategy was tried before the patient was transferred to our hospital even though a chronic PJI was present, the therapy was considered insufficient as well.

### Statistical modelling

The main independent variable in our model was the presence of polymicrobial infections. As potential confounders we included age, gender, BMI, ASA score, THA vs. TKA, systemic inflammatory response syndrome (SIRS) or sepsis, recurrent PJI, duration of infection, local extremity grade (McPherson 1–3) and systemic host grade (McPherson A–C) as well as number of revision surgeries and inadequate antibiotic or surgical therapy [17]. All data were double-checked for errors. All variables were tested for normal distribution using P-P normal probability plots and the Shapiro-Wilk test. All results are presented on the original scale.

A multivariate generalised logistic regression model was used to calculate the odds ratio (OR) of definitively free of infection, clinical resolution of infection and laboratory resolution of infection. All OR are given with 95 % confidence intervals (CI). Age, gender, BMI, ASA score, THA vs. TKA, SIRS or sepsis, recurrent PJI, duration of infection, local extremity grade (McPherson 1–3) and systemic host grade (McPherson A–C) were included as variables in a backward stepwise model, i.e. a full model including all variables was set up and the variable with the lowest strength of association was removed [17]. Subsequently, the model was run again, and again the variable with the lowest strength of association was removed. This process was reiterated until only variables with significant associations with the main endpoints remained. An alpha of 5 % was considered significant. All calculations were done using Stata 10 (StataCorp LP, College Station, TX, USA).

## Results

Definitively free of infection was the first endpoint studied. A univariate logistic regression model including this endpoint and polymicrobial infections showed a significant association ($p$=0.041) with an OR of 0.3 (95 % CI 0.1–1.0). The multivariate logistic stepwise backward regression model allowed only for ASA score (OR 0.4, 95 % CI 0.2–1.0, $p$=0.062) as a borderline significant covariable in the association between polymicrobial infection and definitively free of infection. The adjusted association between polymicrobial infection and definitively free of infection itself was statistically significant with an OR of 0.3 (95 % CI 0.1–0.9) at a $p$ value of 0.031.

The association between polymicrobial infection and definitively free of infection in THA alone was OR of 0.2 (95 % CI 0.04–1.1) at a $p$ value of 0.067 without statistically significant covariables. The adjusted association between polymicrobial infection and definitively free of infection in TKA alone was OR of 0.5 (95 % CI 0.1–2.9) at a $p$ value of 0.414 without statistically significant covariables.

Laboratory resolution of infection was the second endpoint studied. A univariate logistic regression showed a significant association ($p$=0.020) with an OR of 0.1 (95 % CI 0.01–0.7). The multivariate logistic stepwise backward regression model allowed for gender (OR 7.2, 95 % CI 1.2–43.5, $p$=0.032) and ASA score (OR 0.2, 95 % CI 0.1–1.0, $p$=0.046) as significant covariables in the association between polymicrobial infection and laboratory resolution of infection. The adjusted association between polymicrobial infection and laboratory

resolution of infection itself was not statistically significant with an OR of 0.03 (95 % CI 0.0–0.4) at a $p$ value of 0.006.

The adjusted association between polymicrobial infection and laboratory resolution of infection in THA alone was OR of 0.1 (95 % CI 0.01–0.9) at a $p$ value of 0.042, with gender as a borderline significant covariable ($p$=0.058). For TKA the model did not converge because of collinearity between gender and implanted prosthesis.

Clinical resolution of infection was the third endpoint studied. The univariate logistic regression showed another significant association ($p$=0.004) with an OR of 0.1 (95 % CI 0.02–0.5). The stepwise backward model allowed, again, for gender (OR 3.9, 95 % CI 0.8–18.5, $p$=0.092) and ASA score (OR 0.1, 95 % CI 0.01–0.4, $p$<0.001) as significant co-ariables. The adjusted association between polymicrobial infection and clinical resolution of infection itself was not statistically significant with an OR of 0.02 (95 % CI 0.0–0.2) at a $p$ value <0.001.

The adjusted association between polymicrobial infection and clinical resolution of infection in THA alone was OR of 0.03 (95 % CI 0.0–0.4) at a $p$ value of 0.008, with gender as a borderline significant covariable ($p$=0.008). Again, the model did not converge for TKA because of collinearity between gender and implanted prosthesis.

### Number of revision operations necessary

In the univariate analysis there was a significant association between the number of revisions and polymicrobial infection with an OR of 3.2 (95 % CI 1.9–4.5) at a $p$ value of less than 0.001. The stepwise backward model allowed for BMI (OR 0.2, 95 % CI 0.1–0.3, $p$<0.001) as the only significant covariable. The adjusted association between polymicrobial infection and clinical resolution of infection itself was OR 3.1 (95 % CI 1.9–4.3) at a $p$ value of $p$<0.001. The adjusted coefficient for THA alone was 3.4 (95 % CI 1.8–5.0, $p$<0.001) and for TKA alone 2.0 (95 % CI 0.1–3.8, $p$=0.037).

## Discussion

The interaction between different bacteria in the presence of two or more infectious organisms often results in a synergistic effect favouring persistence of infection or colonisation. However, the pathomechanisms and interactions between different bacteria in polymicrobial PJI remain understood poorly [24].

The hypotheses that PJI with polymicrobial infections reduce the cure rate seems rational. However, the literature and data available are limited. Both outcome and potential confounders investigating PJI in the presence of polymicrobial infections are available in a few studies only, which often combine different surgical techniques and treatment strategies [9]. To the best of our knowledge, we present the largest cohort of patients with polymicrobial infections of THA and TKA treated with a two-stage exchange procedure. Our hypotheses were set up to test the effect size of polymicrobial PJI on the overall success rate regarding resolution of infection compared to monomicrobial PJI.

We were able to investigate 77 patients and to show a significant, statistically sizeable adjusted influence of polymicrobial PJI and definitively free of infection with an OR of 0.3 (95 % CI 0.1–1.0) at a $p$ value of 0.041. The multivariate stepwise backward regression model was only able to identify the ASA score (OR 0.4, 95 % CI 0.2–1.0, $p$=0.062) as a borderline significant covariable in the association between polymicrobial infection and definitively free of infection. The adjusted association between polymicrobial infection and definitively free of infection itself was statistically significant with an OR of 0.3 (95 % CI 0.1–0.9) at a $p$ value of 0.031.

The rate of patients graded as definitively free of infection in our study was 87.5 % ($n$=35) for monomicrobial infections vs. 67.6 % ($n$=25) for polymicrobial infections. Our results and the reduced cure rate are consistent with the literature: Marculescu and Cantey reported on a two year cumulative probability of success of polymicrobial PJI of 63.7 % [9], even though they were able to report on 34 patients only, and again only nine of the 34 patients investigated were treated with a two-stage exchange. The authors concluded that the reduced-even though not significantly reduced-success rate in the group of polymicrobial infections was caused by the increased number of gram-negative and multiresistant infectious organisms. This is especially true since Lora-Tamayo et al. were able to identify polymicrobial infections as an independent predictor of outcome within a large multicentre study of PJI [25].

The distribution reported is comparable to the distribution of infectious organisms found in our patients: gram-negative bacteria [8 (21.6 %)] and multiresistant gram-positive bacteria [26 (70.04 %)] were detected more often in the group of polymicrobial PJI. The percentage of polymicrobial infections in the patients investigated was 48 % ($n$=37 of 77). In the literature the incidence of polymicrobial PJI varies from 19 to 37 %. Moran and colleagues reported on a higher percentage of polymicrobial PJI within the early postoperative stage within 90 days after the primary implantation [9, 26].

Multiple risk factors associated with PJI in TKA or THA have been published, i.e. rheumatoid arthritis, diabetes or obesity [27–29]. However, the literature available regarding polymicrobial infections is limited. Marculescu and Cantey were able to identify patients 65 years of age and older, presenting with a soft tissue defect or wound dehiscence and drainage, and those who had prior local irradiation and less

bacteraemia as risk factors predicting polymicrobial infections in a univariate regression [9]. Nevertheless, only age, local would condition and wound drainage remained as independent, non-confounding risk factors associated with polymicrobial infections. We were able to partially support these data.

This is consistent with the literature since Cierny and DiPasquale published comparable results in 43 patients with PJI in THA and TKA [30]. They showed success rates regarding systemic host grade of 91 % for grade A, 66 % for grade B and 24 % for grade C, only.

We could also identify a significant association in the univariant analysis between the number of revision operations necessary and polymicrobial infection with a regression coefficient of 3.2 (95 % CI 1.9–4.5) at a $p$ value of less than 0.001. The stepwise backward model allowed for BMI (OR 0.2, 95 % CI 0.1–0.3, $p<0.001$) as the only significant co-ariable. In comparison, Marculescu and Cantey were not able to identify prior revision surgeries as an independent risk factor [9]. However, the relatively low number of cases ($n=8$) in their cohort has to be taken into consideration.

### Limitations

Our study has potential shortcomings. Although we were able to analyse the data of 37 patients with polymicrobial PJI and 40 patients with monomicrobial PJI only, the absolute number of patients remains low compared to other studies investigating arthroplasty. This limits the statistical potential to provide a more detailed sub-differentiation within the multivariate regression model without devastating effects on power or effect strength. Due to this and the general limitations of a retrospective and descriptive study, the level of evidence remains low. The major limitations should be resolved in a prospective trial design.

## Conclusion

In conclusion, and to the best of our knowledge, we present the largest cohort investigating polymicrobial PJI treated within a two-stage exchange concept. In respect of the limitations of a retrospective study, we were able to show that a proven polymicrobial infection is a independent risk factor regarding resolution of infection. Future prospective trials should focus on the identification of risk factors or predictors associated with polymicrobial infections to provide specialised care for these patients.

**Conflict of interest** The authors declare that they have no conflict of interest.

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