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ORIGINAL PAPER

Synovial aspiration and serological testing in two-stage revision arthroplasty for prosthetic joint infection: evaluation before reconstruction with a mean follow-up of twenty seven months

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Abstract

Introduction The two-stage revision protocol is the gold standard for controlling and treating low-grade prosthetic joint infections of total hip and total knee arthroplasty. The antibiotic pause for diagnostic reasons before reconstruction (stage two) is discussed in relation to the persistence of the infection and the development of resistant bacterial strains. Serological markers and a synovial analysis are commonly used to exclude the persistence of infection. Therefore, we asked (1) is the serological testing of C-reactive protein and leucocytes a valuable tool to predict a persistence of infection? and (2) what is the role of synovial aspiration of Plymethylmethacrylat (PMMA) spacers in hip and knee joints?

Materials and methods One hundred twelve patients who were MSIS criteria-positive for a prosthetic joint infection were studied, including 45 total hip arthroplasties (THA) and 67 total knee artrhoplasties (TKA) patients. All patients were treated with a two-stage-protocol using a mobile PMMA spacer after a 14-day antibiotic-free interval, during which we measured serological markers (C-reactive protein and leucocytes) and performed synovial aspiration (white blood cell count, polymorphonuclear cell percentage, and microbiological culture) in these patients and compared the results with those of their long-term-follow-up (mean follow-up 27 months, range 24–36 months).

Results Of the 112 patients, 89 patients (79.5%; 95% CI 72–86.9) exhibited infection control after a two-stage exchange, and we detected most methicillin-resistant, coagulase-negative Staphylococci (CoNS) in cases of a persistent infection. The mean sensitivity of serum C-reactive protein in the patients was 0.43 (range 0.23–0.64), and the mean specificity was 0.73 (range 0.64–0.82). For serum leucocytes, the mean sensitivity was 0.09 (range 0–0.29), and the mean specificity was 0.81 (range 0.7–0.92). The mean sensitivity for the WBC count in the synovial fluid (PMMA spacer aspiration) was 0.1 (range 0–0.29), and the mean specificity was 0.79 (range 0.68–0.92). For the PMN percentage, the mean sensitivity was 0.1 (range 0–0.29), and the mean specificity was 0.79 (range 0.68–0.92). No cut-off values could be established for C-reactive protein, leucocytes, WBC count and PMN percentage due to the low AUC.

Conclusion No reliable markers were identified for the long-term persistence of infection. C-reactive protein and leucocytes were often elevated, even when the infection was controlled. In addition, normalized serum markers did not exclude the persistence of infection during follow-up. The synovial analysis of the WBC count and PMN percentage did not predict the persistence of infection. However, microbiological synovial fluid analysis is often misleading due to false positive microbiological cultures, which results in overtreatment.

Keywords Prosthetic joint infection · Synovial aspiration · Serological testing · Two-stage protocol

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Introduction

The total number of hip and knee arthroplasties performed in the United States is increasing. With expected growth rates of 673% in total knee arthroplasties (TKA) and 174% in total hip arthroplasties (THA), the cost for revision arthroplasty will become a relevant economic burden, as revision surgery is

expected to double during this period [1]. Prosthetic joint infection is a rare but significant complication after arthroplasty. It still remains one of the major complications after total joint replacement [2].

The challenge in controlling prosthetic joint infection is underscored by projections that suggest a robust increase in THA over the next 15 years [1]. A combination of synovial aspiration and serological markers is considered to be the best available test for determining the presence of prosthetic joint infection after THA and TKA [3–5]. For chronic low-grade infections, a two-stage revision protocol is considered to be the gold standard for infection eradication in North America [6–8]. In the literature, the success rates for TKA vary from 82% to 100%, and those for THA can be up to 90% for two-stage exchange and antibiotic treatment [9, 10]. Different therapeutic strategies, including the use of antibiotic-impregnated PMMA spacers, the duration and type of antibiotic therapy (oral or IV) and the duration of the interval, are available for the two-stage exchange for infected endoprostheses. The duration of the interval varies in the literature from two weeks to 12 weeks [2, 11]. A common interval used in the United States and Europe is a six-week antibiotic treatment that is often followed by a 14-day antibiotic-free interval during which serological testing and synovial aspiration are performed to exclude a persistent infection before the second stage of the reconstruction. This therapeutic regime is usually combined with an antibiotic-impregnated PMMA spacer.

This widely used therapeutic option is controversial in the literature because of the systemic antibiotic pause after six weeks, which may lead to persistence of the infection and the development of multiple drug resistant bacterial strains. However, the accuracy of serological tests and synovial aspiration under ongoing systemic antibiotic therapy is questionable as well.

The data that have been published concerning the value of serological markers and synovial aspiration between the stages show heterogeneous cohorts, short follow-up periods and an inconsistent antibiotic-free interval [12, 13].

No studies have been published that have a long follow-up period. All of the published studies define the persistence of infection as the presence of infection at the time of reconstruction, and therefore, all of the available studies are missing long-term failures.

We therefore asked (1) is the serological testing of C-reactive protein and leucocytes a valuable tool to predict a persistence of infection after a 14-day antibiotic-free interval and before the second stage of reconstruction in THA and TKA? and (2) what is the role of synovial aspiration of PMMA spacers in long-term hip and knee joint arthroplasty infection control after a 14-day antibiotic-free interval before the second stage of reconstruction?

Patients and methods

This retrospective study included all patients who were treated between 1 July 2012 and 31 March 2015 for the diagnosis of a prosthetic joint infection in the clinic for orthopaedic surgery at the Klinikum rechts der Isar of the Technical University of Munich (TUM) in Germany. All cases were managed by a multidisciplinary team consisting of an infectious disease physician, a pharmacist and an orthopaedic surgeon.

A total of 141 patients (58 men and 83 women; 59 hips and 82 knees), with a mean age of 68.3 years (range 21 to 88 years), were included. All patients had a prosthetic joint infection according to the MSIS criteria [14]. Twenty-one patients were excluded (see Fig. 1) because they were considered to not have chronic low-grade infections and were treated with the DAIR procedure (debridement, antibiotics and implant retention). Eight patients were excluded because of death, amputation, spacer exchange or incomplete data sets. The remaining 112 patients (49 men and 63 women; mean age of 67.1 years and range of 21–88 years; 67 knees and 45 hips) were treated using a two-stage interval; a PMMA mobile spacer (Biomet, StageOne Hip and Knee Cement Spacer Molds) was used for TKA patients, and the routine treatment consisted of 160 mL of Palacos with gentamycin and clindamycin, which was enriched with vancomycin (1 g per 20 mL PMMA), for THA patients. After explaining the treatments to the patients, they were treated with organism-specific intravenous antibiotics for a mean of ten days (range 7–14 days), followed by oral antibiotics for four weeks, depending on susceptibility of the strains. After a 14-day pause of antibiotics, sterile synovial fluid aspiration was performed under an X-ray fluoroscopic device (prolonged aerobic, anaerobic and fungal cultures ($n = 92$), white blood cell (WBC; $n = 60$), polymorphonuclear cells (PMN; $n = 60$)), and serological markers were assessed (C-reactive protein, leucocytes and ESR ($n = 112$)). In 20 cases, no synovial fluid was obtained. These cases were excluded from the synovial aspiration group, and reimplantation was performed in all of these cases.

A mean of six intra-operative tissue cultures (range 5–8) were evaluated. Patients were considered to have a persistent infection if two cultures were positive, and the results were compared to those of the pre-operative synovial aspiration cultures.

The patients had a mean follow-up of 27 months, with at least 24 of those months focused on the eradication of the infection.

Subsequently, sensitivities, specificities, positive and negative likelihood ratios and positive and negative predictive values were calculated for C-reactive protein, leucocytes, synovial fluid culture, WBCs, and PMNs. Receiver operating characteristic (ROC) curves were generated to determine the optimal cut-off values for C-reactive protein, the ESR and

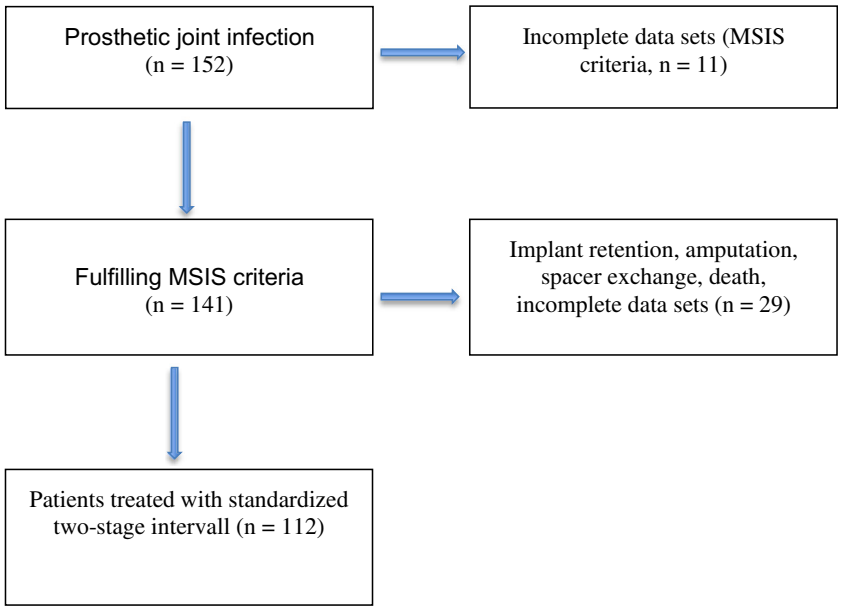

Fig. 1 Flow chart showing patient selection

leucocytes. The area under the curve (AUC) for each ROC curve was determined. All statistical tests were performed using Excel (Microsoft 2010, Redmond, USA) and SPSS (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 20.0., IBM Corp., Armonk, NY).

Results

Of the 112 patients included in the study, 89 patients achieved infection control in the two-stage interval (79.5%; 95% CI 72–86.9%), and 23 patients remained infected (20.5%; 95% CI 13.1–28%) during a mean follow-up period of 24 months (mean follow-up 27 months; range 24–36 months).

Of the patients in the persistent infection group, 16 patients (60.9%; 95% CI 40.9–80.8%) were infected with the same initial bacterial/fungal species. Seven patients (30.4%) had a shift of bacterial strains; they either developed mixed infections, or showed a shift from CNS strains to gram-negative bacteria (see Table 1). Staphylococcus species were responsible for a high percentage of infection (65.2%; 95% CI 45.8–84.7%) in the infection controlled and persistent infection groups (Table 1). Methicillin-resistant coagulase-negative Staphylococci (CoNS) were documented in the majority of persistent infections (62.5%).

A comparison of serum C-reactive protein and serum leucocytes before stage two in both groups showed a mean C-reactive protein level of 1.57 mg/dL (range 0.1–9.8 mg/dL) and a mean leucocyte count of 6.7 g/L (range 4–14.5 g/L) in the persistent infection group, while the mean C-reactive protein level was 0.79 mg/dL (range 0.1–5.5 mg/dL), and the mean leucocyte count was 7.0 g/L (range 3.5–12.5 g/L) in the infection controlled group.

The sensitivity of serum C-reactive protein was 0.43 (range: 0.23–0.64), while the specificity was 0.73 (range 0.64–0.82). For serum leucocytes, the sensitivity was 0.09 (range 0–0.29), and the specificity was 0.81 (range 0.7–0.92).

Table 1 Microorganisms identified causing prosthetic joint infection: bacterial species, number of patients, persistent infections, bacterial shift

Measure	Serum analysis C-reactive protein (CRP)	Serum analysis leucocytes	Aspiration microbiologic culture	Aspiration white blood cell count (WBC)	Aspiration polymorphnuclear cells (PMN)
Sensitivity (95% CI)	0.43 (0.23–0.64)	0.09 (0–0.2)	0.06 (0–0.17)	0.1 (0–0.29)	0.1 (0–0.29)
Specificity (95% CI)	0.73 (0.64–0.82)	0.88 (0.81–0.94)	0.92 (0.86–0.98)	0.81 (0.7–0.92)	0.79 (0.68–0.92)
Positive predictive value	0.29 (0.14–0.45)	0.15 (0–0.35)	0.14 (0–0.4)	0.1 (0–0.29)	0.09 (0–0.26)
Negative predictive value	0.83 (0.75–0.92)	0.79 (0.71–0.87)	0.81 (0.73–0.81)	0.81 (0.7–0.92)	0.81 (0.7–0.92)
Likelihood ratio +	1.61 (0.64–3.59)	0.7 (0–3.66)	0.74 (0–9.18)	0.53 (0–3.71)	0.48 (0–3.06)
Likelihood ratio -	0.77 (0.44–1.2)	1.04 (0.84–1.27)	1.02 (0.85–1.23)	1.11 (0.77–1.55)	1.14 (0.79–1.6)

Table 2 Diagnostic value of different diagnostic tools (C-reactive protein, leucocytes, microbiologic culture, synovial fluid white blood-cell count, percentage of polymorphnuclear cells) before reconstruction in two stage interval

Bacterial species	Number of patients	Persistent	Shift
Staphylococcus aureus (MSSA)	22 (19.6%)	3 (18.8%)	1 (14.3%)
Methicillin-sensitive Coagulase-negative Staphylococci (CoNS)	20 (22.4)	0	1 (14.3%)
MRSA	2 (1.8%)	1 (6.3%)	
Methicilin-resistant Coagulase-negative Staphylococci (CoNS)	27 (24.1%)	10 (62.5%)	
Streptococcus spp.	3 (2.7%)	0	
E. coli	14 (12.5%)	0	
Enterobacter cloacae	4 (3.6%)	1 (6.3%)	2 (28.6%)
Enterococcus faecalis			3 (42.9%)
Pseudomonas	1 (0.9%)	1 (6.3%)	
Serratia spp.	8 (7.1%)	0	
Proteus mirabilis	1 (0.9%)	0	
Micrococcus luteus	1 (0.9%)	0	
Propionibac. acnes	5 (4.5%)	0	
VSE	4 (3.6%)	0	
Totals	112 (100%)	16 (100%)	7 (100%)

The sensitivity for the WBC count in the synovial fluid (PMMA spacer aspiration) was 0.1 (range 0–0.29), and the specificity was 0.79 (range 0.68–0.92). For the PMN percentage, the sensitivity was 0.1 (range 0–0.29), and the specificity was 0.79 (range 0.68–0.92). The sensitivity for microbiological cultures was 0.06 (range 0–0.17), with a specificity of 0.92 (range 0.86–0.98). We demonstrated only one true positive culture among seven positive cultures because six cultures were considered to be false positive. The microbiological cultures were compared to the intra-operative cultures instead of those obtained during the follow-up period. A detailed comparison between the aspirational cultures of WBCs and PMNs is shown in Tables 2 and 3.

Cut-off levels with a balance between sensitivity and specificity could not be calculated due to the low AUC for all ROC curves that were generated for the serum aspiration tests (Fig. 2). The AUC for C-reactive protein serum analysis before reimplantation was 0.631 (range: 0.498–0.764. $p = 0.054$), and the AUC for leucocytes was 0.426 (range: 0.282–0.570, $p = 0.275$). We detected an AUC of 0.355 (range: 0.113–0.597) for the synovial aspiration of PMMA spaceholders and an AUC of for the WBC count and PMN percentage of 0.171 and 0.230 (range: 0.064–0.396), respectively, with no significant difference ($p = 0.011$). The standard deviations and p-values are provided in Table 4.

Table 3 Positive (LR+) and negative (LR-) likelihood ratios and their corresponding effect on posttest probability according to Jaeschke [15]

LR+	LR-	Effect on posttest probability
>10	<0.1	Large
5–10	0.1–0.2	Moderate
2–5	0.2–0.5	Small
1–2	0.5–1	Marginal
1	1	No change

Discussion

The rapid development of PJI shortly after surgery is typically caused by highly virulent bacteria, such as *Staphylococcus aureus*, and associated with acute symptoms, such as pain and fever. In contrast, late manifestations of PJI are often due to a low-grade infection with less virulent bacterial strains of the dermal flora, including coagulase-negative Staphylococci (CNS). These low-grade PJI infections frequently result in septic loosening of the prosthetic components over time.

The two-stage interval is commonly regarded as the gold standard for the treatment of chronic prosthetic joint infections (low-grade PJI). It is considered to be the most definitive strategy in terms of infection eradication and preservation of joint function [8]. Its success rate varies in the literature, but a meta-analysis reported successful treatment in 89% of patients [16–18]. However, at least one in ten patients does not achieve complete infection control. Therefore, different serological and synovial parameters should be used to identify the persistence of an infection before reconstruction (stage two).

Our study is subject to several limitations. The small number of patients that remain infected limits the power of the statistical testing; however, all studies in the latest literature that addresses that problem are facing similar problems. Another limitation is the definition of chronic prosthetic joint infection. Although we used the most common definition in

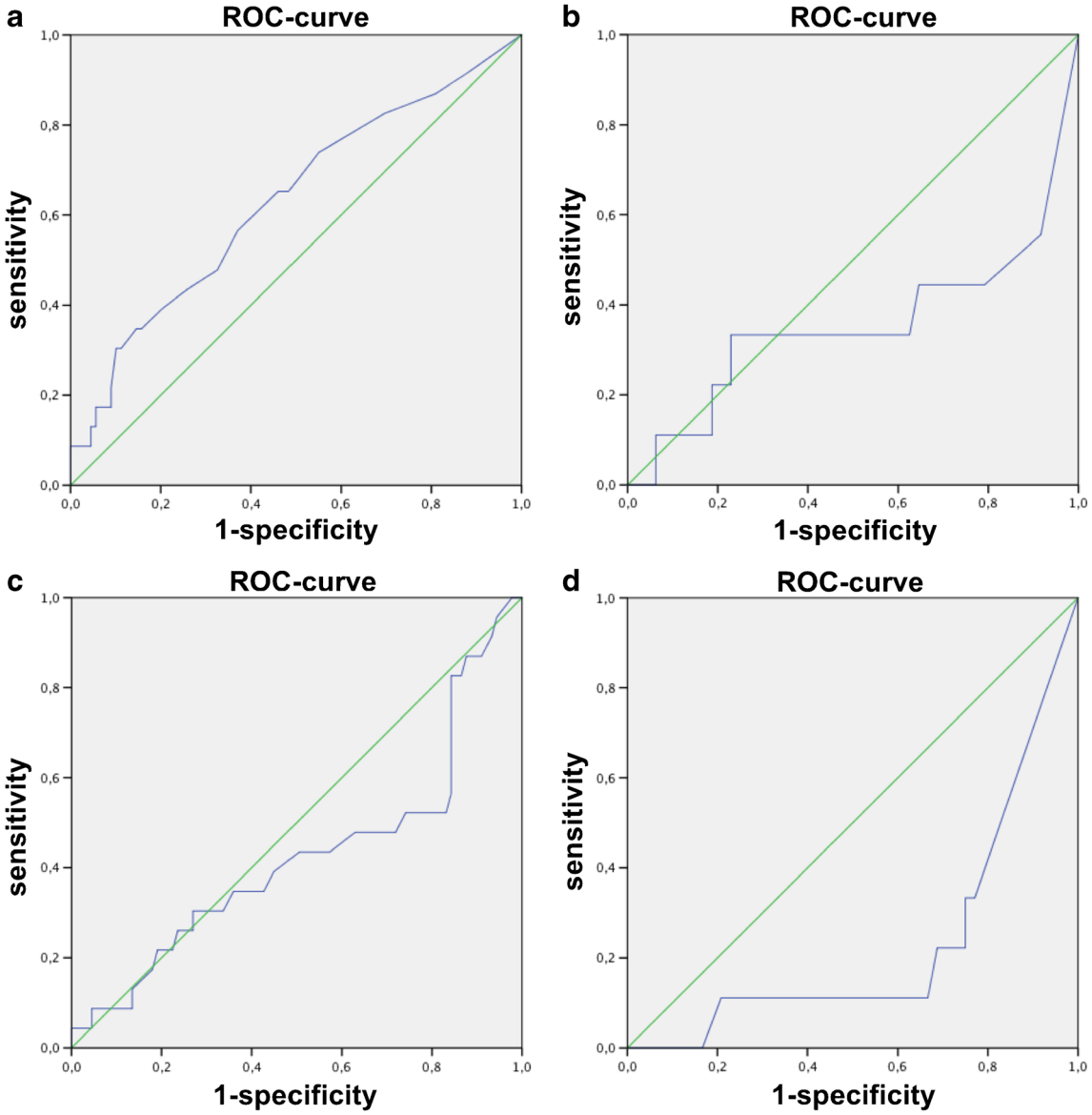

Fig. 2 **a** Receiver-operating-characteristic (ROC) curve demonstrating the serum analysis of CRP (C-reactive protein). **b** Receiver-operating-characteristic (ROC) curve demonstrating the serum analysis of leucocytes. **c** Receiver-operating-characteristic (ROC) curve demonstrating the synovial fluid white blood-cell count (WBC). **d** Receiver-operating-characteristic (ROC) curve demonstrating the synovial fluid percentage of polymorphnuclear cells (PMN)

the MSIS criteria, there is no common sense of definitive criteria of persistent infection in a two stage exchange in literature. Therefore, some patients may be miscategorised applying other than the MSIS criteria.

We were able to evaluate the long-term follow-up for at least 24 months and detect long-term failure, in contrast to Ghanem et al. and Kusuma et al., who defined the persistence of infection as infection present at the time of reconstruction. This led to false negative results in their cohorts, which missed the long-term failures due to the suppression of slow-growing, low virulent organisms at the time of reconstruction.

Regarding our first question, our data demonstrated the poor performance of serum markers (C-reactive protein, leucocytes) in predicting infection control before the second stage (reconstruction). The low sensitivity of serum C-reactive protein in our cohort confirms the findings of Hoell et al., Kusuma et al. and Ghanem et al. [12, 19, 20]. Kusuma et al. noted that their poor results may have been explained by the small number of patients. However, we demonstrated an even lower sensitivity in a cohort with 200% more patients in the group with infection persistence, which suggests that long-term failures were missed in their cohorts. In contrast to our results, Janz et al. reported a surprisingly high sensitivity (95%) with a low specificity (20%) for serum C-reactive protein for predicting the persistence infection of Girdlestone hips without PMMA spacers. We do not have an explanation for

Table 4 Receiver-operating-characteristic (ROC) curve: analysis of all variables

Tested variables	AUC	Standard deviation	p-value	95% Confidence interval
Serum analysisC-reactive protein (CRP)	0.631	0.68	0.054	0.98–0.764
Serum analysisLeucocytes	0.426	0.73	0.275	0.282–0.570
Aspirationwhite blood cell count(WBC)	0.355	0.123	0.171	0.113–0.597
Aspirationpolymorphnuclear cells(PMN)	0.23	0.085	0.011	0.064–0.396

AUC area under the curve

these findings, except that the time between removal of the implant and performance of the second stage was up to several months in the Girdlestone-hip group, whereas our cohort and the cohorts of Kusuna et al. and Ghanem et al. had a standardized timeline with a diagnostic workup eight weeks after explanation. In addition to the poor performance of serum C-reactive protein, we demonstrated an even worse predictive performance of serum leucocytes. Although serum leucocytes are generally known to be an unspecific inflammatory marker and often used in routine serum diagnosis, their determination is not helpful to exclude persistent infection. ROC curve and AUC analysis demonstrated the poor results of these serum parameters, for which cut-off levels that could not be determined due to the low AUC values, which confirmed the results of Ghanem et al. [21].

A common approach to determine when to perform the second stage surgery based on normalization of serum parameters is not recommendable. The reliability of serum markers may increase if the time between the first and second stages is prolonged up to six months or one year, resulting in a poor functional outcome and increased psychosocial burden (Mühlhofer et al. unpublished).

Synovial aspiration and the determination of the WBC count, differential of PMNs and microbiological culture results, show high diagnostic value in identifying prosthetic joint infections before stage one. These markers are considered the gold standard in modern evidence-based diagnostic algorithms.

Regarding our second question, the results of microbiological cultures (long-term incubation) were poor, with a sensitivity of 6% and a high incidence of false positive and false negative cultures. In our cohort, the results were worse than those of Janz et al., who analyzed synovial fluid from Girdlestone hips, and confirmed those of Kusuma et al., who used a much larger cohort [22]. False positive results are especially problematic and may lead to overtreatment with prolonged antibiotic therapy and additional surgery if not evaluated by an interdisciplinary team.

We also observed poor results regarding the quantitative synovial analysis (WBC count and PMN percentage), although these parameters are reliable predictors for prosthetic joint infections before stage one [3, 4]. The WBC count and PMN percentage are not reliable in the synovial analysis of PMMA spacers. Few studies have addressed this question, and we do not agree with Kusuma et al., who postulated that determination of the WBC count and PMN percentage was the best test for predicting infection persistence due to the lower variability of local inflammatory responses. In the long-term follow-up in our cohort, the WBC count and PMN percentage showed a sensitivity of 0.1. The AUC showed that the aspiration of PMMA spaceholders poorly predicts persistent infection in patients undergoing a two-stage interval before reconstruction.

Conclusion

In summary, no reliable marker was identified for indicating the long-term persistence of an infection. C-reactive protein and leucocytes are often elevated even though the infection is controlled. In addition, normalized serum markers do not exclude the persistence of an infection during the follow-up period. The synovial analysis of the WBC count and PMN percentage did not confirm their well-investigated diagnostic reliability before stage one. However, microbiological synovial fluid analysis is often misleading due to false positive microbiological cultures, resulting in overtreatment. We recommend an interdisciplinary approach, emphasizing the need for high quality antibiotic treatment, including biofilm active antibiotics, without any antibiotic pause for diagnostic reasons.

Authors' contributions Conception and design of the study: HM, CK, RvE-R.

Generation and acquisition of the data (2014): HM, CK, FP.

Generation and acquisition of the data (2015): HM, NH, and SF.

Assembly, analysis and/or interpretation of data: HM, CK, FP, RvE-R.

Drafting and revising of the manuscript: HM, SF, CK, FP, NH, RvE-R, and JS.

Approval of the final version of the manuscript: HM, CK FP, SF, NH, JS, and RvE.

All of the authors read and approved the final manuscript.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Abbreviations *PJI*, Prosthetic joint infection; *CoNS*, Coagulase-negative staphylococci; *TKA*, Total knee arthroplasty; *THA*, Total hip arthroplasty; *MRSA*, Methicillin-resistant staphylococcus aureus; *MRSE*, Methicillin-resistant staphylococcus epidermidis; *PMMA*, Polymethylmethacrylate; *MSIS*, Musculoskeletal infection society; *FU*, Follow-up; *CI*, Confidence interval; *AUC*, Area under the curve; *CRP*, C-reactive protein; *WBC*, White blood cell count; *PMN*, Polymorphonuclear cells; *ROC*, Receiver operating characteristic

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