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ORIGINAL PAPER

Poor performance of microbiological sampling in the prediction of recurrent arthroplasty infection

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Abstract During a two-stage revision for prosthetic joint infections (PJI), joint aspirations, open tissue sampling and serum inflammatory markers are performed before re-implantation to exclude ongoing silent infection. We investigated the performance of these diagnostic procedures on the risk of recurrence of PJI among asymptomatic patients undergoing a two-stage revision. A total of 62 PJI were found in 58 patients. All patients had intra-operative surgical exploration during re-implantation, and 48 of them had intra-operative microbiological swabs. Additionally, 18 joint aspirations and one open biopsy were performed before second-stage reimplantation. Recurrence or persistence of PJI occurred in 12 cases with a mean delay of 218 days after re-implantation, but only four pre- or intraoperative invasive joint samples had grown a pathogen in cultures. In at least seven recurrent PJIs (58%), patients had a normal C-reactive protein (CRP, <10 mg/l) level before re-implantation. The sensitivity, specificity, positive predictive and negative predictive values of pre-operative invasive joint aspiration and CRP for the prediction of PJI recurrence was 0.58, 0.88, 0.5, 0.84 and 0.17, 0.81, 0.13, 0.86, respectively. As a conclusion, pre-operative joint aspiration, intraoperative bacterial sampling, surgical exploration and serum inflammatory markers are poor predictors of PJI recurrence. The onset of reinfection usually occurs far later than reimplantation.

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Introduction

A two-stage revision is an acknowledged procedure for the treatment of infected arthroplasties (PJI) [1]. Infection recurrence after re-implantation harbours significant morbidity [2, 3], and every effort should be made to identify patients at risk of such a devastating complication. Normally, an interval of eight weeks is required between infected implant removal and reimplantation, although there are no uniform recommendations about the duration of this interval, ranging from two to four weeks [1] to several months [4, 5]. For patients undergoing an antibiotic-free window before re-implantation, the interval between two stages may be divided into a six-week course of antibiotic treatment [3], followed by at least two additional weeks of an antibiotic-free window [1, 3, 6]. A minimal delay of at least two weeks seems to be important, because it has been shown that periprosthetic tissue culture sensitivity is less than 50%, if antimicrobial therapy was discontinued less

than 14 days before sampling [5]. In the absence of clinical signs and the presence of normal serum inflammatory markers [6], re-implantation is undertaken. Additionally, a joint aspiration or open biopsy is often performed before re-implantation [3] to exclude asymptomatic persistent infection. However, this empirical approach in PJI management is mostly based upon speculation and experts' recommendations, rather than scientific evidence.

Recently, Müller et al. evaluated the values of serum C-reactive protein (CRP) and pre-operative joint aspiration in the predilection of persistent infection [7]. The utility of CRP was equally assessed among 109 patients undergoing second-stage reimplantation for infected knee prostheses [8]. Both studies found only a poor or moderate performance for both methods.

In this study, we investigate PJIs that recurred after a two-stage revision with an emphasis on the utility of pre-operative joint aspiration, serum inflammatory markers, intra-operative sampling, surgical exploration and histology obtained during re-implantation.

Materials and methods

Setting

The Geneva University Hospitals is a tertiary centre for Orthopaedic Surgery and Traumatology. The Orthopaedic Service has 132 acute care beds, a dedicated Infectious Diseases physician [9] and performs more than 500 arthroplasties annually. The Service conducts a hip and knee arthroplasty registry with active post-discharge surveillance [10]. One day of hospitalisation costs roughly US $1200. A surgical tissue sampling for bacterial testing costs $6,500 (including anaesthesia, occupation of the operating theatre, nursing, medical treatment and analyses). The expenses for CRP sampling and leukocyte counts are about $10 each. The cost for the treatment of a single episode of PJI is about $45,000.

Study design

We performed a single-centre retrospective analysis from January 1996 to June 2009. We included all PJI cases treated by two-stage revision with a minimal follow-up of six months post-reimplantation. Two physicians (M.S. and I.U.) independently collected 61 variables for each PJI. Definition of PJI required pus around the affected arthroplasty and/or at least three identical pathogens in microbiological samples. We collected all CRP samples between explantation and re-implantation with the exception of patients with other causes of serum CRP alterations (i.e. active neoplasm, autoimmune disease, cirrhosis Child B and C). The CRP follow-up of the individual patients under antibiotic treatment was stratified in weekly periods during the first three weeks. The CRP value at the end of each week post-explantation ± one day, e.g. after seven days, or after 14 days post-explanation, was noted on an EXCEL sheet. In contrast, CRP samples performed within 15 days preceding re-implantation were defined as pre-implantational samples. The normal upper limits for CRP, total leukocyte count, and left shift were given by our accredited laboratory and set for <10 mg/l, <10 G/l, and <5% of non-segmented neutrophils, respectively.

Microbiological assessment procedures were unchanged during the study period. They were based on the Clinical and Laboratory Standards Institute's recommendations [11]. For direct microscopic examination Gram and Acridine-staining were used. Histology (obtained during reimplantation without frozen section) was considered positive if pathogens were detected or if the sample revealed at least ten neutrophils per high-power field. There was no ethical committee approval necessary.

Statistical methods

We investigated potential clinical risk factors for recurrent PJI. To avoid model overfitting and spurious results, no multivariate analysis was performed. Group comparisons between PJI with and without recurrence were performed by the Wilcoxon-rank sum or the Fisher exact test, as appropriate. P values ≤ 0.05 (all two-tailed) were significant. STATA™ software (9.0, STATA Corp, College Station, USA) was used.

Results

General and microbiological results

A total of 62 PJI, treated with a two-stage exchange procedure, were found in 58 patients (mean age 68 years; 29 women). Patients were followed-up for an average of 3.3 years after reimplantation. The PJI involved hip arthroplasties (n=36, 58%), knee arthroplasties (n=23, 37%), hip hemiarthroplasties (n=2), and one shoulder arthroplasty. The pathogens were *Staphylococcus aureus* (n=15, of which four were methicillin-resistant), coagulase-negative staphylococci (n=18), streptococci (n=15), *Enterococcus faecalis* (n=1), anaerobes (n=2), Gram-negative aerobic bacteria (n=7), and culture-negative PJI (n=4). In 32 cases (32/62, 52%), patients were immunocompromised by diabetes mellitus (n=8), severe alcoholism (n=7), neoplasms (n=6), steroid medication for autoimmune disease (n=3), HIV (n=1), or affected by a

combination of several immunosuppressive diseases listed above ($n=7$).

Treatment procedure

The median duration of antibiotic therapy after prosthesis explantation was 44 days (range, 28–105 days). In 54 PJI (54/62, 87%), antibiotics had been stopped after an average of 109 days (range, 2–634 days) before re-implantation; in 41 cases this window lasted more than 14 days. The prolonged antibiotic-free windows were due to organisational difficulties, patient's comorbidities, and social problems rather than problems related to infection. In eight cases (8/62, 13%), re-implantation took place during ongoing antibiotic treatment. During the prosthesis-free interval, a gentamicin-loaded spacer was used in ten of 23 knee PJIs (43%). For an additional 11 knee PJIs (48%), a spacer without antibiotic loading was used. For all hip PJIs, explantation without transient spacer was the treatment of choice.

Recurrence of PJI

In 12 cases (12/62, 19%), PJI recurred after reimplantation with a mean and median delay of 218 and 88 days, respectively (Table 1). All PJI were surgical site infections without evidence for haematogenous origin. All recurrences were given postoperative antibiotic treatment for a median duration of 46 (range, 9–93) days. Six recurrences were successfully treated with debridement and arthroplasty retention. In three cases, patients underwent another two-stage exchange. A second recurrence did not occur for these nine cases. One case was treated with lifelong suppressive antibiotic treatment and two cases were lost to follow-up.

Microbiological sampling before re-implantation

A total of 19 invasive diagnostic procedures were performed in 18 patients before re-implantation (18/62, 29%) including 18 joint aspiration procedures (median 33 days before re-implantation, range 0–205 days) and one open biopsy (126 days before). No iatrogenic complications were observed as a result of these invasive procedures (Table 1).

Intraoperative Gram-staining

A total of 48 PJI episodes (48/62; 77%) underwent intraoperative Gram- and Acridine orange staining during re-implantation (average 3.3 samples). In all but one case, the samples were free of leucocytes and staining failed to reveal pathogens. The only exception was a recurrent PJI due to *S. aureus* (last case of Table 1). This case was also the only one revealing clinical pus at the operation site among all study patients (1/62; 1.6%).

Intraoperative cultures

In three cases, the presence of bacteria was interpreted as true pathogens, since they were identical to those responsible for the PJI and were subsequently treated with antibiotics. In one case, *Corynebacterium* sp (one of four samples) was interpreted as contamination and was not treated with antibiotics after reimplantation.

In summary, in 53 of 62 PJI, an invasive microbiological sample before reimplantation was performed. Among these, 48 episodes (48/53, 91%) had an antibiotic-free interval longer than 14 days (13/19 preoperative invasive samples, and 35/48 intraoperative invasive samples).

Performance of various tests

In summary, in seven recurrent PJIs (7/12, 58%), pre-reimplantational aspiration, open biopsy, intra-operative surgical status and intra-operative cultures were negative. For these invasive diagnostic procedures altogether, the sensitivity, specificity, positive predictive and negative predictive values for recurrent PJI were 0.58, 0.88, 0.5, and 0.84, respectively (Table 2).

Histology

A total of 18 re-implantations were accompanied by histology. No histological sample revealed the presence of pathogens but four showed marked inflammation (4/18, 22%). Sensitivity, specificity, positive and negative predictive values for recurrent PJI were 0.33, 0.8, 0.25, and 0.86, respectively (Table 2).

Serum inflammatory markers before reimplantation

Total leukocyte count was elevated in three cases (mean value 6.2 G/l; median three days before reimplantation). Neutrophil left shift was always within normal range.

Pre-reimplantational serum CRP levels (mean value 10.0 mg/l; range 1–54 mg/l) were sampled in 42 cases (42/62; 68%; median three days before reimplantation). In eight of them, CRP values were above normal limit. Among eight patients without normalisation of CRP levels before reimplantation, one had recurrent infection and seven did not (Fisher exact-test, $p=1.0$). In seven recurrent PJIs (58%), patients had a normal C-reactive protein (CRP, <10 mg/l) level before re-implantation. Sensitivity, specificity, positive predictive and negative predictive values of elevated CRP levels for recurrent PJI were 0.17, 0.81, 0.13, and 0.86, respectively (Table 2).

Table 1 Overview of 12 recurrent arthroplasty infections after two-stage exchange

Arthroplasty	Gender, age (years)	Pathogen	Antibiotics[a]	Antibiotic-free interval[b]	CRP[c]	Aspiration/biopsy[d]	Intraoperative samples (during reimplantation)	Recurrence	Recurrent pathogen
Hip	F, 80	*E. faecalis*	93 days	14 days	4 mg/l	Four days before, negative	*E. faecalis* (1/4 samples)	46 days later	*E. faecalis*
Knee	F, 52	Unknown	35 days	14 days	4 mg/l	One day before, negative	Negative (0/1 sample)	379 days later	*unknown*
Hip	M, 70	*S. epidermidis*	28 days	16 days	n.a.	n.a.	Negative (0/2 samples)	27 days later	*S. hominis*
Hip	M, 37	*P. aeruginosa*	84 days	585 days	6 mg/l	n.a.	Negative (0/3 samples)	One day later	*P. aeruginosa*
Knee	M, 89	*Streptococ. sp*	42 days	33 days	3 mg/l	n.a.	Negative (0/3 samples)	313 days later	*Streptococcus* sp
Knee	F, 90	*S. aureus*	90 days	14 days	n.a.	30 days before, negative	Negative (0/1 sample)	629 days later	*S. aureus*
Knee	M, 77	*S. milleri*	92 days	14 days	n.a.	Four days before, negative	Negative (0/3 samples)	Ten days later	*S. milleri*
Hip	F, 62	*S. mitis*	46 days	60 days	23 mg/l	n.a.	*Corynbacterium* (1/4 samples)	645 days later	*S. mitis*
Hip	M, 70	*E. faecium*	90 days	13 days	5 mg/l	n.a.	*E. faecium* (1/3 samples)	One day later	*E. faecium*
Knee	M, 61	*S. lugdunensis*	42 days	12 days	6 mg/l	One day before, negative	Negative (0/4 samples)	645 days later	*S. lugdunensis*
Hip	M, 32	*S. aureus*	56 days	73 days	n.a.	n.a.	*S. aureus* (1/3 samples)	129 days later	*S. aureus*
Hip	M, 33	*S. aureus*	42 days	221 days	2 mg/l	One day before, positive	No immediate reimplantation	One day later	*S. aureus*

M male, *F* female, *CRP* C-reactive protein

All *Staphylococcus aureus* infections were methicillin- and rifampin-susceptible

[a] Duration of antibiotic treatment before re-implantation

[b] Delay between end of antibiotic treatment and reimplantation

[c] Last C-reactive protein before re-implantation

[d] Time of joint aspiration before re-implantation

Table 2 Performances of diagnostic procedures before re-implantation of arthroplasties

Diagnostic	Recurrence of arthroplasty infection	No recurrence of arthroplasty infection[a]
Invasive samplings[b]		
Presence of pathogens	5	5
Absence of pathogens	7	36
Serum C-reactive protein levels		
10 mg/l and more	1	7
Normal values	5	29
Serum total leukocyte counts		
10 G/l and more	0	3
Normal values	4	47
Histology from invasive samples		
Inflammation	1	3
No inflammation detected	2	12

[a] After re-implantation

[b] Pre-operative needle aspiration before re-implantation, biopsies and intra-operative microbiological sampling

CRP values throughout the antibiotic treatment

In the interval between explantation and reimplantation, a total of 366 CRP samples were performed in the study population without concomitant causes of serum CRP alteration. After starting antibiotic treatment, CRP values fell 90% within a mean of 30 days and a median of 20 days (range, 6–93 days) and returned to normal within a mean of 38 days and a median of 27 days (range, 9–93 days). The patient populations with and without recurrent PJI after reimplantation did not differ in post-explantational peak values (median 208 mg/l vs. 172 mg/l, Wilcoxon rank sum test, $p=0.65$), time until CRP normalisation (median 35 days vs. 19 days, Wilcoxon rank sum test, $p=0.20$) or delay until 90% decrease of initial CRP values (median 26 days vs. 16 days, Wilcoxon rank sum test, $p=0.13$). The median CRP levels at the end of each week during the first three weeks post-explantation did not differ between infected vs. uninfected patients (all Wilcoxon-rank sum tests; $p>0.20$).

Comparisons between PJI episodes with and without recurrences

Neither group differed according to key parameters (Table 3).

Discussion

We report a poor performance of pre-operative invasive microbiological sampling, intraoperative surgical exploration, or pre-reimplantational serum inflammatory markers for recurrent infections among asymptomatic patients undergoing a two-stage revision. None of the patients presented signs of persistent infection during the antibiotic-free window, regardless of duration, while awaiting re-implantation. No clinical parameter showed specific association with recurrence (Table 3). Our recurrence risk of 19% was similar to the 20% published by Hanssen and Osmon [12], the 21% indicated by Ghanem et al. [8] and to other reports of two-stage [3, 13] or one-stage exchanges [14, 15], even if lower recurrence rates have also been reported [6, 16]. Therefore, we would exclude a substantial therapeutic bias.

The landmark publication of Zimmerli et al. cites that at least three intraoperative tissue specimens should be sampled for culture [1], which is common practice, although some experts ideally recommend up to six specimens [17]. In our study population, the average number of intraoperative microbiologic samples was 3.3, and only a quarter of all reimplantations revealed less than three samples (Table 1). Therefore we equally exclude a major sampling bias.

Recurrent PJI occurred far later than the reimplantation procedure and was solely detected on the basis of patient's complaints. While our average delay of recurrence was seven months after reimplantation, it was 13 months [2] or 66 months [6] in other reports. We think that the usual six-week antibiotic course may heal, or at least suppress infection, to such a low level that current standard laboratory procedures might not be able to detect them. Pathogens need time to recover and to provoke recurrent clinical infection. It is likely that the length of the antibiotic-free window would not play a major role, since these pathogens may remain dormant for years in the absence of a new implant, and are awakened only in the presence of a new one; a phenomenon observed in recurrent osteomyelitis [18].

The low accuracy of intraoperative Gram-staining in PJI diagnosis has been previously reported [19]. Additionally, Müller et al. evaluated the values of preoperative cultures in

Table 3 Comparison between the groups presenting arthroplasty infection recurrence vs. cure after a two-stage revision

All episodes(n=62)	No recurrence(n=50)	Recurrence(n=12)	Odds ratio, 95% confidence interval	p value[a]
Patients				
Female sex	25 (50%)	4 (33%)	0.5, 0.1–2.2	0.35
Median age	71 years	66 years		0.39
Chronic immunosuppression[b]	27 (54%)	5 (42%)	0.6, 0.1–2.6	0.53
Median ASA-score	2 points	2 points		0.10
Hip arthroplasty compared to knee arthroplasty	29 hips (62%)	7 hips (58%)	0.3, 0.1–2.6	1.0
Infection				
Median delay between primary arthroplasty and infection	883 days	623 days		0.63
Median delay between infection and explantation	12.5 days	6.5 days		0.24
Presence of bacteremia	11 (22%)	1 (8%)	0.3, 0.1–2.7	0.43
Infection caused by *Staphylococcus aureus*	11 (22%)	4 (33%)	1.8, 0.3–8.2	0.46
Infection caused by coagulase-negative staphylococci	17 (34%)	2 (17%)	0.4, 0.1–2.2	0.31
Infection caused by *Streptococcus* sp	12 (24%)	3 (25%)	1.1, 0.2–5.2	1.00
Infection caused by Gram-negative pathogens	6 (12%)	1 (8%)	0.7, 0.1–6.5	1.00
Before reimplantation				
Median duration of antibiotic treatment	43 days	51 days		0.71
Use of spacers	28 (56%)	9 (75%)	2.4, 0.5–15.0	0.33
Use of antibiotic-loaded spacers	14 (28%)	6 (50%)	2.6, 0.6–11.3	0.18
Median duration of antibiotic free window	56 days	25 days		0.53
Median last C-reactive protein value	6.0 mg/l	4.5 mg/l		0.59
Median last total leukocyte count	6.0 G/l	7.5 G/l		0.08
Median percentage of non-segmented neutrophils	1%	1%		0.89

[a] Group comparisons were performed with the Wilcoxon rank sum test or the Fisher exact test, as appropriate

[b] Diabetes mellitus, transplant patient, chronic alcoholism, neoplasia, HIV infection, steroid treatment for autoimmune disease, dialysis

the diagnosis of PJI [7]. Interestingly, their sensitivity, specificity, positive and negative predictive values were 0.57, 0.5, 0.78 and 0.29, respectively. While our sensitivity level was similar to theirs (0.58), specificity and negative predictive values were better (0.88 and 0.84, respectively). Of note, the study by Müller et al. investigated a heterogeneous group of 50 patients with suspected PJI, while in our retrospective study, invasive joint aspiration has been performed in proven, formerly severe infections upon reimplantation [7]. Thus, we initially expected a bias towards a higher likelihood of detection of persistent infection than reported for first time diagnosis. This was not the case, which was also found by Mont et al., who prospectively assessed infected knee arthroplasties with a two-stage exchange and pre-revisional cultures in one arm and none in the other. Statistically, the "overall infection rate" was not significantly different between both groups (5/35 vs. 3/34 of recurrence) [3].

It is questionable whether normal serum inflammatory markers are to be expected or required prior to reimplantation after long-lasting antibiotic treatment [8]. Ghanem et al. retrospectively determined the value of erythrocyte sedimentation rate and CRP serum levels before second-stage reimplantation by receiver operating characteristic curves (ROC). They attributed a poor performance to both markers for the predilection of persistent infection. Cut-off values could not be obtained because of high variance [8]. In contrast, Greidanus et al. prospectively assessed 151 knee arthroplasties and determined a CRP cut-off of 13.5 mg/l for PJI with a sensitivity and specificity of 91% and 86%, respectively [20]. However, they only assessed the accuracy for first-time PJI diagnosis and not the accuracy for the detection of persistent infection after treatment, which represents a different clinical situation. In a trial with children with acute osteomyelitis, the peak CRP value was reached on day 2. The decrease was very rapid,

with normal values reached within a week (mean 6.9 days) [21]. Another paediatric study found a normalisation time of serum CRP levels of only ten days during the treatment of childhood bone and joint infections [22]. In adults, few authors have investigated serum CRP levels with the clinical response of surgical site infections after spinal surgery. Although the CRP levels of patients at the four-week-antibiotic treatment time point were lower than in patients that healed well (mean CRP 0.3±0.5 mg/l) as opposed to those with overt persistent infection (continuing drainage, erythema; mean CRP 7.3±3.5 mg/L), CRP values returned to normal within a few days [23]. In our study, CRP values tended to decrease more rapidly during antibiotic treatment in patients without recurrent infections than in patients with recurrent PJI. However, these differences were not significant. To our best knowledge, there are currently no prospective trials on serum inflammatory markers in the predilection of persistent infection after antibiotic treatment before second-stage reimplantation. As for the accuracy of peripheral leukocyte counts, previous reports failed to demonstrate a correlation with osteo-articular infections [21, 24].

Our report has several limitations. First, it is a single-centre retrospective study with a small number of cases, limiting the general application of the results. Second, our patients had quasi normal CRP and total leukocyte counts preceding reimplantation. It could be that higher values would predict PJI recurrence. However, in these cases, patients are also likely to be symptomatic. Third, histology and PCR were not sampled in all cases. Only in five PJIs was PCR used. Because of this small number, we excluded PCR from analysis. In the literature, PCR may enhance sensitivity for first-time diagnosis of PJI [25]. However, its value in the setting of pre-reimplantational sampling after prolonged antibiotic treatment is not yet established, unlike histology for which a high accuracy has been attributed in this context [7]. Fourth, although rare, infection by a new pathogen (instead of mere recurrence) may also occur after a two-stage exchange of PJI. It is debatable whether these new infections should be counted as recurrences as we did in our study. This issue is only sparsely reported in literature [6]. Fifth, no multivariate analysis was performed to avoid overfitting and spurious results. Thus, we cannot allow and adjust for potential confounding factors.

As a conclusion, the benefit of pre-reimplantational invasive cultures in the absence of clinical signs is probably too small compared to its expense. Even when negative, these cultures give no guarantee for absence of future recurrence [3]. Further reports or trials are needed for these invasive tests. For CRP as the hallmark and the best among currently available clinical serum inflammatory markers [26], a prospective trial during two-stage exchange is warranted.

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