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Periprosthetic Joint Infection

Lead Guest Editor: Bernd Fink
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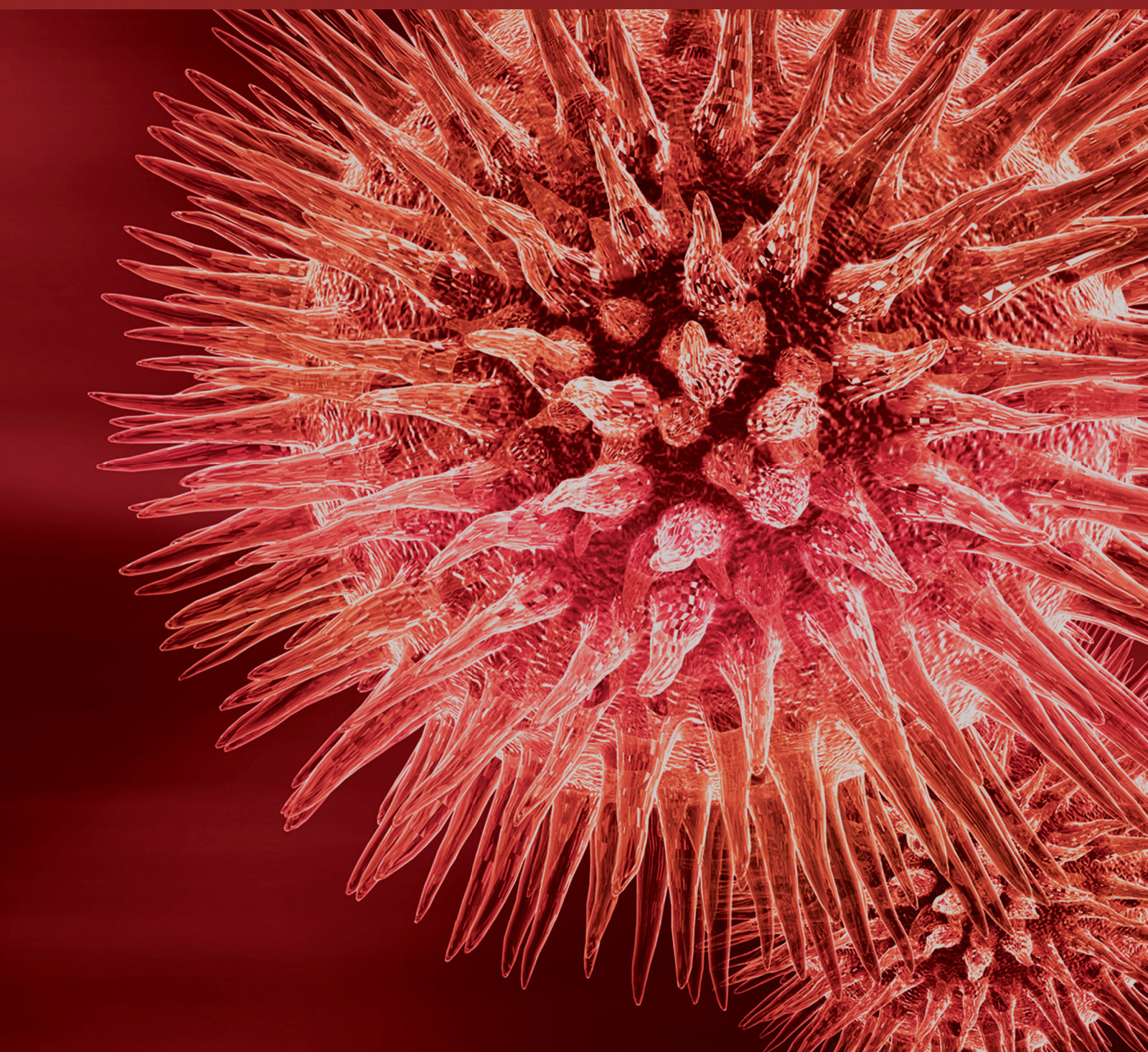

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Editorial

Periprosthetic Joint Infection

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The periprosthetic infection (PPI) of hip, knee, and shoulder endoprostheses is, with an incidence of around 1%, an uncommon but nevertheless devastating complication of arthroplasty procedures [1, 2]. The classification proposed by Tsukayama et al. [3] differentiates between acute early and chronic late infections whereby the threshold between the two is 4 weeks after the surgical intervention. However, other authors regard infections occurring up to 3 months after surgery as early infections [4, 5]. Acute periprosthetic infections that arise after many trouble-free years as a result of an infection at a remote site are classified as acute hematogenous infections and are treated in the same way as acute early infections [3].

When early infections occur, within 4 weeks of implantation, the implant can be left in place with a high probability of cure whereas late infections require prosthesis revision to eradicate the infection [6]. In such cases, one can differentiate between one-stage and two-stage revisions. Two-stage revision involves an initial operation to remove all foreign materials and this is followed by an interim phase of mostly 6–12 weeks, either left as a Girdlestone situation or with the implantation of a cement spacer.

Whereas early infections, i.e., those occurring within the first four weeks of implantation, usually cause local and systemic inflammatory reactions, these are often missing in cases of late periprosthetic joint infection with low-grade symptoms, occurring later than four weeks after implantation [3]. This makes the diagnosis of late periprosthetic infections very much more difficult. The classical clinical signs, laboratory tests, and imaging techniques such as X-ray and scintigraphy are associated with a high level of false positives and false negatives [7].

A preoperative diagnostic before revision surgery takes place is helpful because therapeutic strategy differs in septic revisions from aseptic revision; local and systemic antibiotic therapy can be planned specifically before surgery takes place and can be started at a time before new biofilm formation on a new prosthesis has taken place [1, 2].

There are many questions pertaining to both the diagnostic of periprosthetic joint infection (PJI) and its treatment and existing procedures are based more on empirical findings than on data from prospective studies with a high level of evidence. This special issue on periprosthetic joint infection discusses important details in the diagnostic and therapeutic procedures.

Even though the detection of the microorganism causing the periprosthetic joint infection is the most important diagnostic tool, the paper of D. Karczewski et al. shows that the indication for a septic revision can also solely be based on the intraoperative (para-)clinical signs fistula or purulence, Krenn–Morawietz histological type 2 or 3, and joint aspirate > 2000/μl leukocytes or >70% granulocytes. The paper of G. Bori et al. gives an update about the histopathology in periprosthetic joint infection. The paper of S.-J. Lim et al. underline that the preoperative CRP on its own does not have a strong power for the diagnostic of PJI by showing that patients with a hip fracture and an elevated CRP have higher CRP-levels also postoperative compared to those with normal

CRP values without having a higher risk for PJI. S. P. Boelch et al. show in their paper that the aspiration of the joint with a spacer in a two-stage procedure of an infected total knee arthroplasty for cultivation of the aspirate is not helpful for the decision whether an reimplantation can be done or not.

For the topic of treatment of PJI the other paper of S. P. Boelch et al. reported that Copal® cement and Palacos® R+G cement for the use as gentamicin and vancomycin biantibiotic-loaded spacer have comparable elution levels of the antibiotics out of the spacers. D. H. Ro et al. could show that periprosthetic joint infection does not preclude good clinical outcomes after a revision total knee arthroplasty. However, poor outcomes were mainly associated with large bone defects and an increased number of previous surgeries. In a systemic review and meta-analysis M. Reisener and C. Perka found out that culture-negative PJIs have comparable outcomes than culture-positive PJIs. However, B. Zatorska et al. could show that the production of extracellular DNA of *Staphylococcus epidermidis* in 24 hours biofilms correlates with the patients' outcome "not cured" after 12 months. However, for *Staphylococcus aureus* infections no such correlation was detected. If two-stage revisions failed M. Faschingbauer et al. detected that irrigation and debridement have a chance of 63.2% of success and may therefore be an therapeutical option for acute reinfections after failed two-stage revisions if performed within the first 30 postoperative days or if symptoms are present for less than 3 weeks. For the reimplantation in two-stage septic revisions F. Reichel et al. showed that tranexamic acid is effective for the reduction of blood loss.

B. Fink and F. Sevelda worked out the specific diagnostic and therapeutic particularities for periprosthetic joint infections of the shoulder.

Conflicts of Interest

The editors declare that they have no conflicts of interest regarding the publication of this special issue.

Acknowledgments

We thank Dr. Mark E. Shirtliff for his coediting work on this special issue. During this activity he left us suddenly and unexpectedly. We are deeply saddened by this great loss.

Bernd Fink
Konstantinos Anagnostakos
Heinz Winkler

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Clinical Study

Reducing Blood Loss in Revision Total Hip and Knee Arthroplasty: Tranexamic Acid Is Effective in Aseptic Revisions and in Second-Stage Reimplantations for Periprosthetic Infection

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Introduction. The aim of the study was to determine the usefulness of tranexamic acid (TXA) in revision total hip arthroplasty (rTHA) and revision total knee arthroplasty (rTKA). We analyzed the perioperative blood loss with and without TXA in aseptic rTHA and rTKA as well as in second-stage reimplantation for hip and knee periprosthetic infection. *Materials and Methods.* In this prospective cohort study, 147 patients receiving TXA (96 rTHA, 51 rTKA) were compared to a retrospective cohort of 155 patients without TXA (103 rTHA, 52 rTKA). The TXA regimen consisted of a preoperative bolus of 10 mg/kg bodyweight (BW) TXA plus 1 mg/kgBW/h perioperatively. Given blood products were documented and the perioperative blood loss was calculated. Thromboembolic events were registered until three months postoperatively. In subgroups, the effects of TXA were separately analyzed in 215 aseptic revisions as well as in 87 reimplantations in two-stage revisions for periprosthetic infection. *Results.* Both TXA groups showed a significantly reduced mean blood loss compared to the respective control groups. The TXA group of rTHA patients had a mean blood loss of 2916 ml ± 1226 ml versus 3611 ml ± 1474 ml in the control group ($p<.001$). For the TXA group of rTKA patients, mean calculated blood loss was 2756 ml ± 975 ml compared to 3441 ml ± 1100 ml in the control group ($p=.0012$). A significantly reduced blood loss was also found in the TXA subgroups for aseptic and septic revision procedures. No thromboembolic events were recorded among the TXA groups. *Conclusions.* There is a significant reduction of perioperative blood loss under TXA influence without an increased incidence of adverse events. The standard use of TXA can be recommended in aseptic hip and knee revision arthroplasties as well as in second-stage reimplantations for periprosthetic infection.

1. Introduction

Revision arthroplasty procedures are mostly associated with higher blood loss than primary implantations [1]. Subsequently, there is a greater demand for allogeneic blood transfusion during and after these operations [2]. Even though blood transfusions today are safer than in the past, they are still accommodated by adverse events like allergic reactions or other negative side effects [3]. The transfusion of allogeneic blood products may be associated with adverse patient outcome as well as increased morbidity and mortality [4, 5]. In arthroplasty procedures, blood transfusions have been reported to be a risk factor for periprosthetic infection [6].

For patient safety and economic reasons a variety of methods to minimize the use of blood products have been developed and summarized under the concept of patient blood management [7–9]. Particularly, one of the antifibrinolytic agents, tranexamic acid (TXA), has been studied broadly in recent years. A significant impact on perioperative blood conservation in primary hip and knee arthroplasty without increasing the risk of thromboembolic events has

been reported [10–25]. However, there is only minimal literature on the effect and complication rates of TXA in revision procedures, including septic revisions.

Therefore, the purpose of this study was to evaluate if the usage of TXA in revision hip and knee arthroplasty (i) reduces the perioperative blood loss, (ii) lowers the intra- and postoperative transfusion rates, and (iii) does not increase the rate of deep vein thrombosis (DVT) or pulmonal embolism (PE).

2. Material and Methods

We performed a prospective cohort study after establishing a standard operating procedure (SOP) for the use of tranexamic acid in our department. Starting in July 2015, every patient undergoing revision total hip arthroplasty (rTHA) or revision total knee arthroplasty (rTKA) received a bolus of 10 mg/kg bodyweight (BW) TXA as well as a continuous dose of 1 mg/kgBW/h intraoperatively. The patients received the bolus prior to skin incision. Up to December 2016, 96 rTHA patients and 51 rTKA patients could be included in this study. The inclusion criteria were patients undergoing any type of aseptic revision of one or more prosthetic components (except isolated liner exchange) or reimplantation in a two-stage procedure for periprosthetic infection. The explantation procedures for periprosthetic infection were not included. Patients with allergy to TXA, a history of thromboembolic events, or DVT/PE were excluded from the study. The inclusion and exclusion criteria were identical in the TXA- and no-TXA-group.

Revision procedures from January 2014 to June 2015, before starting the SOP, were used as retrospective control group. Each prospective cohort of revision patients receiving TXA was compared to a retrospective cohort without TXA. In this manner, 96 prospectively collected rTHA patients with TXA were compared to 103 retrospectively collected rTHA patients without TXA application. Likewise, the prospectively assessed 51 rTKA patients receiving TXA were compared to 52 retrospectively assessed rTKA patients who did not receive TXA.

Subgroup analyses were carried out to examine the effect in aseptic revisions and in reimplantation procedures separately.

From the patients' records, the following parameters were investigated: the operative procedures, the preoperative blood levels of hemoglobin as well as on postoperative days one, three, and five, hematocrit, and creatinine, including hemostasis indicators (international normalized ratio, partial thromboplastin time, antithrombin, and fibrinogen) as well as the operative risk factors like preoperative anemia, history of thromboembolic events, infection, fracture, tumor, and cardiac, renal, or pulmonary dysfunction. The risk factors were represented by the ASA score [26]. Furthermore, given blood products and the postoperative occurrence of complications were registered. The main outcome variables were the calculated blood loss as well as the thromboembolic complications like DVT and PE.

The perioperative blood loss was calculated according to the Brecher formula [27]. Variables required for the computation are the patient's blood volume, the preoperative hematocrit (Ht), the Ht at the postoperative day 5 (POD 5), and all given blood products including intraoperative cell salvage. Patient's blood volume was calculated using height, weight, and gender of the patient [28, 29]. Compared to other methods used for the assessment of perioperative blood loss, the Brecher formula is one of the few methods that take the so-called hidden blood loss into account [27].

The perioperative thrombosis prophylaxis included a daily dose of 40 mg enoxaparin given subcutaneously to all patients for a minimum of 28 days beginning on postoperative day 1. Patients presenting clinical signs for DVT were examined using Doppler ultrasound. Suspected PE were diagnosed or ruled out via CT pulmonary angiography. Any complication was recorded during a follow-up period of three months postoperatively.

All surgical procedures were performed by 10 senior surgeons. Reimplantations in two-stage exchange procedures were performed 6-12 weeks after explantation and antibiotic spacer implantation. If a tourniquet was used in rTKA procedures, it was placed at the level of the upper thigh and inflated to 350 mm Hg prior to cementing the prosthetic components. The tourniquet was deflated after wound closure and application of compression dressing.

Data was collected using the hospital information system. The statistical analyses were performed using SPSS 22 (IBM Corporation, Armonk, NY). Descriptive analysis was carried out and distribution diagrams were used to control for Gaussian distribution. Levene's test assessed the equality of the variances of the given variables.

Student's t-test was used to compare means between the TXA and no-TXA groups if normal distribution and equal variances were present. Welch's test was used if no equal variances were found. Mann-Whitney U test was applied if no normal distribution was encountered. Cross tabulation was used for nominal scaled variables like the complication frequency. For all tests, two-sided significance was assumed for p values below .05. Post hoc computed power analyses for the t-tests of the mean blood loss were carried out for rTHA and rTKA groups (.999 and .912).

The study was approved by the Ethics Committee of the University under the number S-413/2014 and registered at the Federal Institute for Drugs and Medical Devices filed under the number NIS 3377. Therefore, it is in accordance with the ethical standards on human experimentation.

3. Results

Between January 2014 and December 2016, a total of 517 rTHA or rTKA were performed at our institution. 215 patients had to be excluded because either patients did not receive TXA according to the protocol or patients received TXA for individual reasons prior to the start of the SOP. The remaining 199 patients undergoing rTHA and 103 patients undergoing rTKA could be included in the study. The preoperatively recorded demographic data and blood variables showed no statistically significant differences between the TXA group and the no-TXA group (Table 1).

Table 1: Demographic data and preoperative blood variables. Given are mean values (SD), except the absolute amounts for female gender.

Demographic data	TXA Revision THA n=96 Revision TKA n=51	No TXA Revision THA n=103 Revision TKA n=52	p-value
Age [years]			
Revision THA	66.1 (13.5)	68.6 (11.3)	0.16†
Revision TKA	65.3 (15.2)	66.1 (12.4)	0.78
Female gender, N (%)			
Revision THA	57 (59%)	56 (54%)	0.48
Revision TKA	26 (51%)	28 (54%)	0.77
Height [m]			
Revision THA	1.69 (0.11)	1.69 (0.10)	0.68
Revision TKA	1.70 (0.10)	1.69 (0.11)	0.57
Weight [kg]			
Revision THA	76.6 (16.1)	77.6 (18.6)	0.69
Revision TKA	85.2 (21.2)	88.0 (22.3)	0.51
Calculated blood volume [ml]			
Revision THA	4943 (870)	4865 (877)	0.86
Revision TKA	5205 (948)	5265 (1070)	0.77
ASA score			
Revision THA	2.52 (0.78)	2.48 (0.58)	0.65†
Revision TKA	2.47 (0.64)	2.44 (0.57)	0.81
Preoperative Ht			
Revision THA	0.386 (0.051)	0.388 (0.047)	0.71
Revision TKA	0.391 (0.053)	0.391 (0.041)	0.97
INR preop.			
Revision THA	1.01 (0.07)	1.01 (0.07)	0.51
Revision TKA	1.01 (0.06)	1.01 (0.06)	0.71

TXA, tranexamic acid; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists; Ht, hematocrit; INR, international normalized ratio; SD, standard deviation; †Welch's test

For the rTHA group, the most common indication for revision was aseptic loosening of one or more components. Half of the patients presented with this diagnosis. The second most common reason for rTHA was infection or septic loosening with 22% in the TXA-group. 10% of patients were revised because of periprosthetic fracture in the TXA-group and 8% because of hip dislocation. In contrast, the most common indication in the rTKA group was infection beforehand with 41% in the TXA-group, followed by aseptic loosening with 35%. Between the TXA group and the no-TXA group, there were no significant differences concerning the indications for revision surgery (p=.43 for rTHA and p=.25 for rTKA).

Almost one-third of all cases were reimplantations in two-stage revisions for periprosthetic infection. In rTHA and rTKA, the numbers of exchanged components showed no statistically significant differences between the TXA group and the no-TXA group (p=.69 and p=.06, Table 2).

Regarding the use of a tourniquet in the rTKA groups, we found a statistically significant reduced application in the TXA-group with 55% vs 86% in the no-TXA-group (p=.01).

We found a statistically significant decrease in mean calculated blood loss with the usage of TXA in rTHA and rTKA (Table 3, Figures 1 and 2). In rTHA patients, calculated blood loss was 2916 ml ± 1226 ml with TXA compared to 3611 ml ± 1474 ml without TXA (p<.001). In rTKA patients, a blood loss of 2756 ml ± 975 ml with TXA was calculated compared to 3441 ml ± 1100 ml without TXA (p=.0012). Revision THA patients receiving TXA showed a significant higher Ht on POD 5 (p=.03) as well as a statistically significant lower amount of transfused packed red blood cells (RBC, p=.04) than rTHA patients without TXA.

No thromboembolic events were registered in the no-TXA rTKA group and both TXA groups. One patient undergoing a rTHA without TXA was diagnosed with pulmonal embolism. Therefore, no statistically significant difference regarding the thromboembolic events was found between the TXA and the no-TXA groups.

3.1. Subgroup Analysis. Four separate subgroup analyses were carried out to determine if the blood sparing effect of TXA could be registered for aseptic revisions in THA and TKA

Table 2: Revised components.

Components being revised	TXA Revision THA n=96 Revision TKA n=51	No TXA Revision THA n=103 Revision TKA n=52	p-value
Revision THA			0.63
Acetabular component	43	43	
Femoral component	22	26	
Both components	10	16	
Reimplantation of both components in two-stage revisions	21	18	0.44
Revision TKA			0.06
Femoral component	9	2	
Tibial component	1	3	
Both components	20	20	
Reimplantation of both components in two-stage revisions	21	27	0.28

TXA, tranexamic acid; THA, total hip arthroplasty; TKA, total knee arthroplasty; ∗: significant; †: Welch's test.

Table 3: Main outcome variables. Given are the mean values (SD), in addition to minimum, maximum, and median for surgical time.

Outcome variables	TXA Revision THA n=96 Revision TKA n=51	No TXA Revision THA n=103 Revision TKA n=52	p-value
Revision THA			
Surgical time [min]	152.6 (51.6)	150.0 (63.7)	0.7500
Min; Max; Median	50; 290; 150	60; 420; 130	
Ht POD 5	0.288 (0.029)	0.278 (0.029)	0.0300∗
INR postop.	1.09 (0.07)	1.08 (0.07)	0.4700
RBC postop. [unit]	1.00 (1.11)	1.41 (1.49)	0.0280∗†
RBC transfused total [unit]	1.49 (1.62)	2.01 (1.92)	0.0400∗
Transfusion rate	0.57 (0.50)	0.65 (0.48)	0.2600†
Calc. blood loss [ml]	2916 (1226)	3611 (1474)	0.0004∗
DVT/PE	0/0	0/1	-/0.3500
Complication rate	0.21 (0.41)	0.15 (0.36)	0.2700†
Revision TKA			
Surgical time [min]	175.1 (43.5)	174.0 (53.5)	0.9100
Min; Max; Median	105; 300; 165	120; 360; 163	
Ht POD 5	0.279 (0.037)	0.274 (0.025)	0.3800†
INR postop.	1.09 (0.07)	1.11 (0.09)	0.2200
RBC postop [unit]	0.78 (1.15)	1.13 (1.37)	0.1600
RBC transfused total [unit]	1.18 (1.57)	1.54 (1.66)	0.2600
Transfusion rate	0.47 (0.50)	0.58 (0.50)	0.2900
Calc. blood loss [ml]	2756 (975)	3441 (1100)	0.0012∗
DVT/PE	0/0	0/0	-/-
Complication rate	0.23 (0.43)	0.29 (0.46)	0.5300

TXA, tranexamic acid; THA, total hip arthroplasty; TKA, total knee arthroplasty; POD, postoperative day; Ht, hematocrit; INR, international normalized ratio; RBC, packed red blood cells; DVT, deep vein thrombosis; PE, pulmonal embolism; ∗: significant; †: Welch's test.

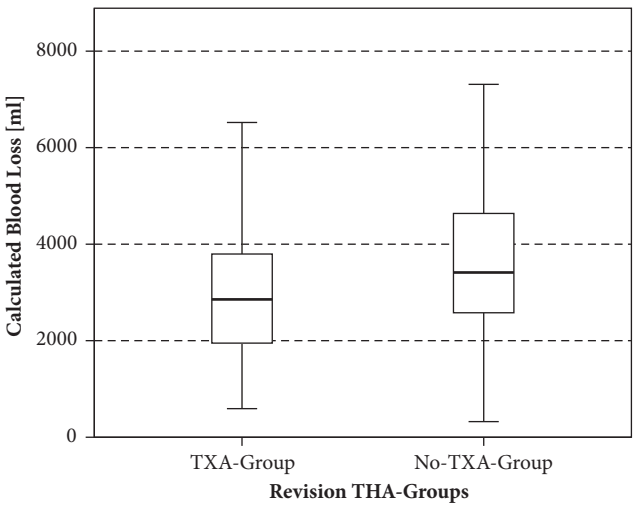

Figure 1: Calculated blood loss of the revision THA groups.

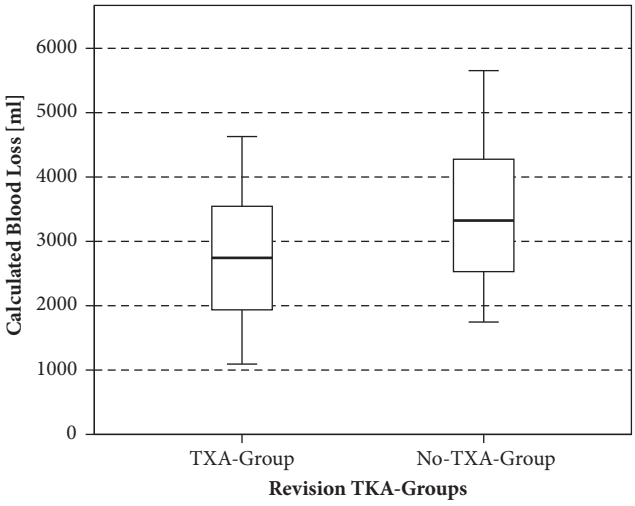

Figure 2: Calculated blood loss of the revision TKA groups.

as well as in hip and knee reimplantations for periprosthetic infection.

The demographic data of all four subgroups showed no significant difference between the TXA and no-TXA groups.

Regarding the aseptic revisions, the blood loss in the TXA groups of aseptic rTHA and aseptic rTKA was significantly decreased (2740 ml ± 1220 ml vs. 3342 ml ± 1304, $p<0.01$ and 2411 ml ± 979 vs. 3053 ml ± 957, $p<0.05$). The Ht on POD5 was significantly higher in both TXA groups and the total amount of transfused RBC in the TXA group of the rTHA patients was significantly lower (Table 4).

Regarding the reimplantations in two-stage exchange procedures, the blood loss in the TXA groups of reimplantation THA and TKA was significantly decreased (3544 ml ± 1052 vs. 4882 ml ± 1604, $p<0.01$ and 3249 ml ± 744 vs. 3801 ml ± 1117, $p<0.05$; Table 5). No reinfection occurred in the TXA or no-TXA groups within 12 months postoperatively.

4. Discussion

The results of the present study suggest that the use of TXA reduces blood loss in rTHA and rTKA without increasing the risk for thromboembolic events. The use of TXA was effective and safe, regardless of whether aseptic revisions or reimplantations in two-stage exchange procedures for periprosthetic infection were analyzed.

Substantial blood loss is one of the main issues in orthopaedic surgery, leading to an increased complication rate and the need for transfusion [9, 30]. Thus, a variety of methods like the use of TXA have been developed for minimizing blood loss.

In contrast to the abundant literature regarding TXA use in primary THA and TKA, there are only a few studies to this date examining the impact of TXA in either rTHA or rTKA [31–38]. All studies reported a benefit of TXA in revision arthroplasty without an increase in complication rates, but had specific limitations, which the current study tried to surpass. Most of the previous authors excluded reimplantations or revisions for septic loosening. For rTHA, only Kazi et al. included second-stage revision procedures into their study plan with a limited number of six reimplantations in the TXA group and six reimplantations in the control group [31]. In rTKA, Smit et al. presented data in which revision for septic loosening was not excluded, including 57 reimplantations in the TXA group and 24 in the control group [37]. Waddell et al. used a topical administration of TXA before wound closure in 20 patients with infected TKA in the first-stage revision (explantation and antibiotic spacer placement) and in 28 patients in the second-stage revision (reimplantation) [39].

To our knowledge, the current study is the first one which includes aseptic revisions as well as reimplantations in two-stage exchange procedures of THA and TKA. Unlike most of the previous authors, we recorded a high number of cases and excluded only isolated liner exchange procedures because of the expected minor blood loss. With this heterogeneity, our patient cohort reflects the everyday spectrum of a center for revision surgery.

All previous revision arthroplasty studies reported a decrease in blood loss related parameters like hemoglobin drop, transfusion rate, or transfused RBC. Our study can support and strengthen this statement finding that TXA decreased the calculated total blood loss. Moreover, we registered a significant lower amount of transfused RBC as well as a significant higher Ht on POD 5 in the TXA group of rTHA patients. There was a tendency for a decreased transfusion rate and decreased transfused RBC in the TXA group of rTKA patients although not reaching statistically significant difference. The tendency for reduced transfusions and a higher postoperative Ht on POD5 results in the significant statistical difference of calculated blood loss because they are both part of the Brecher calculation formula.

For rTKA only a statistically significant difference for the calculated blood loss and not for transfused RBCs was found. The reduced application of a tourniquet in the TXA-group might have had an influence here. Although the minimum

Table 4: Main outcome variables of the subgroup analysis between aseptic revisions. Given are the mean values (SD), in addition to minimum, maximum, and median for surgical time.

Outcome variables	TXA aseptic rTHA n=75 aseptic rTKA n=30	No TXA aseptic rTHA n=85 aseptic rTKA n=25	p-value
Aseptic rTHA			
Surgical time [min]	151.1 (52.7)	140.0 (50.6)	0.1790†
Min; Max; Median	50; 290; 150	60; 270; 125	
Ht POD 5	0.290 (0.031)	0.280 (0.029)	0.0453∗
RBC transfused total [unit]	1.19 (1.39)	1.73 (1.74)	0.0320∗
Transfusion rate	0.51 (0.50)	0.61 (0.49)	0.1833
Calc. blood loss [ml]	2740 (1220)	3342 (1304)	0.0031∗
Complication rate	0.24 (0.43)	0.12 (0.33)	0.0550†
Aseptic rTKA			
Surgical time [min]	163.0 (38.9)	169.0 (46.8)	0.6056
Min; Max; Median	105; 260; 150	120; 255; 165	
Ht POD 5	0.295(0.038)	0.276 (0.025)	0.0290∗†
RBC transfused total [unit]	1.03 (1.73)	1.20 (1.58)	0.7132
Transfusion rate	0.37 (0.49)	0.48 (0.51)	0.4056
Calc. blood loss [ml]	2411 (979)	3053 (957)	0.0178∗
Complication rate	0.25 (0.44)	0.25 (0.44)	1.0000

TXA, tranexamic acid; rTHA, revision total hip arthroplasty; rTKA, revision total knee arthroplasty; POD, postoperative day; Ht, hematocrit; INR, international normalized ratio; RBC, packed red blood cells; DVT, deep vein thrombosis; PE, pulmonal embolism; ∗: significant; †: Welch's test.

Table 5: Main outcome variables of the subgroup analysis between reimplantations. Given are the mean values (SD), in addition to minimum, maximum, and median for surgical time.

Outcome variables	TXA Reimplantation THA n=21 Reimplantation TKA n=21	No TXA Reimplantation THA n=18 Reimplantation TKA n=27	p-value
Reimplantation THA			
Surgical time [min]	157.9 (48.1)	196.9 (94.1)	0.1239
Min; Max; Median	90; 290; 150	110; 420; 175	
Ht POD 5	0.280 (0.023)	0.268 (0.029)	0.1964
RBC transfused total [unit]	2.57 (1.91)	3.33 (2.22)	0.2571
Transfusion rate	0.81 (0.40)	0.83 (0.38)	0.8517
Calc. blood loss [ml]	3544 (1052)	4882 (1604)	0.0035∗
Complication rate	0.10 (0.31)	0.28 (0.46)	0.1173†
Reimplantation TKA			
Surgical time [min]	192.4 (44.9)	178.6 (59.5)	0.3804
Min; Max; Median	130; 300; 180	120; 360; 160	
Ht POD 5	0.256 (0.020)	0.271 (0.025)	0.0273
RBC transfused total [unit]	1.38 (1.32)	1.85 (1.70)	0.3015
Transfusion rate	0.62 (0.50)	0.67 (0.48)	0.7388
Calc. blood loss [ml]	3249 (744)	3801 (1117)	0.0464∗†
Complication rate	0.21 (0.41)	0.33 (0.48)	0.3846

TXA, tranexamic acid; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists; Ht, hematocrit; INR, international normalized ratio; SD, standard deviation; †Welch's test.

clinically important difference for blood loss is unclear, we believe that every reduction in blood loss is beneficial.

Previous authors except Kazi et al. did not calculate the absolute perioperative blood loss and reported only indirect blood loss related parameters as main endpoints. Kazi et al. used the formula according to Gross et al. but were unable to find a difference between the TXA and the control group for the calculated blood loss in a relatively small number of 60

patients [31, 40]. We determined the overall blood loss of the procedures according to the Brecher formula which includes the hidden blood loss postoperatively and is thought to be an accurate measurement [41–43]. This may be the reason for the slightly higher calculated blood loss of the present study compared to previous publications using different calculating methods [41].

Concerning the postoperative complications, Kazi et al. were the only authors who did find a small increase in thromboembolic events for TXA patients without reaching statistical relevance. However, their small patient collection must be considered where only a few events can have a significant impact. In contrast, the current study can underline the findings of all other authors that no increased thromboembolic complications or complications overall were registered.

Regarding the systemic TXA-regime the present study is in line with most of previous studies. The range of total TXA applicated was between 10 mg/kgBW given by Samujh et al. and 3 g given by Noordin et al., who did not report a strict application regime [34, 36].

There are several limitations in our study. The study was not prospectively randomized; in fact a prospective study group of revision cases receiving TXA was compared to a retrospective one without TXA. A relevant number of patients (215/517) had to be excluded from the present study either because they did not receive TXA according to the protocol due to individual reasons or because TXA was applied prior to the start of the SOP. Septic explantations as the first step of two-stage revision procedures could not be included in our study because TXA was only used in reimplantation procedures during the time of this study.

Revision arthroplasty cohorts are naturally heterogenous. Yet, the preoperative data of our collective showed no difference between the TXA and the no-TXA groups. Even the surgical time, as one of the main indicators for blood loss, was not significantly different between the TXA and no-TXA groups. The large range of surgical times reflects the underlying heterogeneity in revision arthroplasty procedures.

Furthermore, we did not include patients with a history of DVT or PE in our study which might lessen the applicability of the general statement that TXA does not increase the risk for thromboembolic events. To this date, studies including high risk patients are still missing. Due to ethical reasons we could not perform a randomized, controlled trial in our revisions whereas the benefits of TXA in primary arthroplasty surgery as well as in other fields of surgery have been well documented. There are still concerns regarding the safety of TXA application in morbid patients. Surprisingly, data to support these concerns are nonexistent.

5. Conclusion

We conclude that TXA is a viable tool to decrease the absolute perioperative blood loss in aseptic revision procedures of THA and TKA as well as in second-stage reimplantations for periprosthetic infection. The use of TXA reduces blood transfusions and does not increase thromboembolic complications. TXA can be recommended as a standard routine for aseptic revisions and reimplantation procedures. Future investigations are warranted to clarify if TXA can also be safely administered to thromboembolic high-risk patients and if so whether or not topical use of TXA may be an alternative.

Data Availability

The original data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the university and registered at the Federal Institute for Drugs and Medical Devices.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Bacterial Extracellular DNA Production Is Associated with Outcome of Prosthetic Joint Infections

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In a retrospective study the association of the production of extracellular DNA (eDNA) in biofilms of clinical staphylococcal isolates from 60 patients with prosthetic joint infection (PJI) and the clinical outcome were investigated. Data from a previous study on eDNA production determined in 24-hour biofilms of staphylococcal isolates (*Staphylococcus aureus* n=30, *Staphylococcus epidermidis* n=30) was correlated with the patients' clinical outcome after 3 and 12 months. Statistical analysis was performed using either the Spearman's rank correlations test or the t-test. eDNA production of *S. epidermidis* in 24-hour biofilms correlated with the patients' outcome 'not cured' after 12 months. For *S. aureus* no such correlation was detected. Thus, eDNA may be a virulence factor of *S. epidermidis*. Quantification of eDNA production as a surrogate marker for biofilm formation might be a potential predictive marker for the management of PJI.

1. Introduction

Periprosthetic joint infections (PJI) are most challenging complications of orthopedic implant surgery. With the rapidly increasing number of implanted prostheses, the impact of PJI is steadily increasing. The relative incidence ranges between 2% and 2.4% of total hip (THA) and total knee arthroplasties (TKA) [1]. The pathogenesis of PJI is associated with the formation of bacterial biofilms involving the tissue around the implant and implant surfaces. Biofilm formation is a bacterial strategy to survive under adverse conditions [2]. The production of extracellular polymeric substances (EPS) protects bacteria against environmental damage. Moreover, bacteria coated by EPS are also able to escape the innate immune response [3]. Generally, biofilms with EPS production enable exchange of genes between the tightly packed bacterial cells. Moreover, their altered metabolic state leads to resistance to antibiotics and consequently persistence of infection and treatment failure [4]. About two-thirds of implant-associated infections in orthopedic surgery are caused by two staphylococcal species: *S. aureus* and *S. epidermidis* [5].

Staphylococci have different mechanisms to form biofilms, which depend on environmental conditions. The most common pathway used by *S. epidermidis* is the production of polysaccharide intercellular adhesin (PIA). PIA is actively induced through stress conditions, such as, e.g., shear flow, and heat, and enhances EPS production [6]. When bacteria were previously exposed to antibiotics, increased production of extracellular DNA (eDNA) was shown to enhance the physical properties of EPS and biofilms resistance to antibiotics [7, 8]. eDNA is released either by active secretion or

by cell autolysis and was shown to be linked to the ability of bacteria to take up DNA from the environment. This feature called competence contributes to the strategy to survive in the environment. [9]. The production of eDNA is regulated by the bacterial population density in response to the accumulation of quorum sensing signals of the closely packed bacterial cells [10]. eDNA binds with other biofilm polymers (*i.e.*, polysaccharides and proteins), thus securing structural stability of the biofilm, and favors bacterial adhesion to abiotic surfaces [11]. Targeting eDNA might be a strategy for the treatment of implant-associated infections and other biofilm associated infections [7, 12, 13].

In a previous study, the time course of eDNA production in biofilms of clinical isolates of *S. aureus* and *S. epidermidis* was studied. The amount of eDNA (mean % area eDNA) was visualized and quantified using confocal laser scanning microscopy (CLSM) and TOTO™-1 staining. Image J software was used to score the images of stained biofilms.

eDNA production was greater in clinical isolates of *S. epidermidis* and *S. aureus* isolated from PJI compared to eDNA production of control isolates from the skin of healthy volunteers. After 24 hours, the amount of eDNA was greater in biofilms of *S. epidermidis* than in biofilms of *S. aureus*. The production of eDNA varies extensively during the time course of biofilm development, as well as the respective staphylococcal species [14].

The aim of the present study was to retrospectively investigate a possible association of eDNA production of in vitro biofilms of *S. aureus* and *S. epidermidis* clinical isolates from patients with PJI and the outcome of the treatment of PJI. The clinical outcomes after 3 and 12 months and the amount of eDNA production of the respective staphylococcal isolates in 24-hour biofilms were correlated. Additionally other influencing parameters like age, weight, the Charlson index for comorbidity (CCI), the site of the infection, and laboratory infection parameters including C-reactive protein, fibrinogen, and leukocyte count were studied.

2. Material and Methods

2.1. Study Design. The study population of this retrospective study was a previous study population whose pathogens, 60 clinical *S. aureus*, and *S. epidermidis* isolates from infected hip and knee prosthesis were examined for eDNA production [14].

The ethics committee of the Medical University of Vienna Austria approved the study protocol (Ethic committee no.: 19025).

2.2. Patient Characteristics. Patients' data were retrospectively retrieved from the electronic patient records. Information was collected and anonymously processed using the University of Vienna Research documentation and analysis platform (RDA, research documentation, and analysis). Patients' characteristics included age, weight, and body-mass-index (BMI). Comorbidities were collected and categorized using the Charlson Comorbidity Index; (Comorbidity-Adjusted Life Expectancy, CCI) [15] (Table 1). Implant indwelling time was also collected and infection classification (Table 2) was performed accordingly. Additionally inflammatory markers such as C-reactive protein (CRP), fibrinogen, and number of leucocytes were assessed at the time of diagnosis of PJI and three weeks thereafter.

The clinical outcomes after 3 and 12 months were defined as (1) cured if patients were able to walk, no further antibiotic treatment and pain medication were needed and neither local nor systemic signs of infection were present, (2) not cured, if patients continued taking antibiotics in order to cure or suppress infection or were planned for another revision surgery, or (3) deceased (Table 3). PJI were classified into early (onset < 1 month after implantation surgery), delayed (onset 3-24 months after surgery), or late infections (onset > 24 months after surgery) [16].

Table 1: Patient's demographic data and health index.

Patients description	n=60
Age	
17-89 years	mean 69
Sex	
female	33 (55%)
male	27 (45%)
BMI (kg/m2)	
underweight (< 19)	2 (3,3%)
Normal (19 - < 25)	19 (31%)
overweight (25 - < 30)	24 (40%)
obesity (>30)	14 (3,3%)
Comorbidities-Charlson Index	
0	8 (13,3%)
1	16 (26,7%)
2	19 (31,7 %)
3	5 (8,3 %)
4	4 (6,7 %)
5	2 (3,3%)
6	3 (5%)
7	2 (3,3%)
12	1 (1,7%)

Table 2: Characteristics of implant infect classification with regard to bacterial species or explanted joint.

	Microorganism		Joint	
	S. aureus	*S. epidermidis*	hip	knee
	n = 30	n = 30	n = 29	n = 31
Implant classification				
primary	23 (76.7 %)	13 (43.3%)	16 (53.3 %)	20 (66.7 %)
secondary (>2)	7 (23.3 %)	17 (56.7%)	14 (46.7 %)	10 (33.3 %)
Infect classification				
early	12 (40 %)	-	5 (16.7 %)	7 (22.6 %)
late	18 (60 %)	-	11 (36.7 %)	8 (26.7 %)
chronic	-	30 (100%)	14 (46.7 %)	15 (50 %)

Table 3: Outcome classified with regard to bacterial species or explanted joint type.

	Microorganism		Joint	
	S. aureus	*S. epidermidis*	hip	knee
Outcome after **3 months**	n=25	n=28	n=23	n=30
cured	16 (64%)	22 (79%)	17 (74%)	21 (70%)
not cured	6 (24%)	5 (18%)	3 (13%)	8 (27%)
dead	3 (12%)	1 (4%)	3 (13%)	1 (3%)
Outcome after **12 months**	n=21	n=27	n=21	n=27
cured	18 (86%)	22 (81%)	18 (86%)	22 (81%)
not cured	3 (14%)	4 (15%)	2 (10%)	5 (19%)
dead	0 (0%)	1 (4%)	1 (5%)	0 (0%)

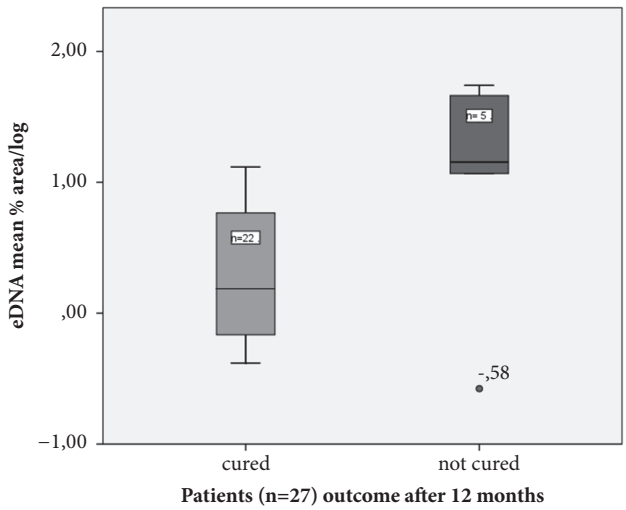

Figure 1: eDNA production in 24h biofilms of *S. epidermidis* is greater in isolates of patients with adverse outcome than in patients with favourable outcome.

2.3. Antimicrobial Susceptibility. Antimicrobial susceptibility testing to cefoxitin, gentamicin, erythromycin, clindamycin, fusidic acid, tetracycline, fosfomycin, trimethoprim, linezolid, mupirocin, and tigecycline was performed in all staphylococcal isolates [14] using disc diffusion tests according to the protocols of European Committee on Antimicrobial Susceptibility Testing (EUCAST) (http://www.eucast.org/clinical_breakpoints/).

The multiple antibiotic resistance (MAR) index was calculated for all tested isolates according to the expression [17]

$$\text{MAR} = \frac{a}{(b * c)} \quad (1)$$

where "a" is the aggregate antibiotic resistance score of all isolates, "b" is the number of antibiotics, and "c" is the number of isolates. The MAR of all tested isolates was 0,183. According to [18] a MAR index of 0.183 indicates that the aggregate antibiotic resistance is low; i.e., the isolates were in general susceptible to the tested antibiotics.

2.4. Statistical Methods. Spearman's rank correlation and the t-test were used to assess parallels in eDNA production, antibiotic resistance, patients clinical conditions, and outcomes. A p-value of <0.05 was considered to be statistically significant. eDNA values were log-transformed and checked for normal distribution before applying the t-test to calculate the approximate log-normal distribution. Calculations were performed using IBM®-SPSS® Version 24.0 (IBM Corp. Armonk. NY. USA).

3. Results

Sixty patients (27 male, 33 female) with a mean age of 69 year (range 17-89, median 71) were included into the study. The two age outliers, 17 and 20 year old patients, suffered from Ewing's sarcoma- or osteosarcoma and received total replacements of the femur and the knee. Thirty-eight of 60 (63.3%) patients were classified as overweight or obese with a BMI > 25 kg/m^2: 24/60 (40%) patients were overweight and 14/60 (23.33%) were obese, (Table 1). After 12 months, the outcome in 40/48 patients was classified as cured, and the outcome in 8 patients was classified as not cured including a patient who died from the infection. A more detailed description of the outcomes with regard to pathogens or type of prosthesis is given in Table 3. A PJI considered as chronic infections were caused by *S. epidermidis*. Early or acute late infections were caused by *S. aureus* (Table 2). Twelve patients were lost during follow-up: 8 patients due to incomplete datasets and 4 patients died from their comorbidities or other age-related diseases (57-84 years; median 75 years old) during the observation period.

3.1. eDNA Production and Clinical Outcome. There was a correlation between the amount of eDNA in 24 h *S. epidermidis* biofilms and patients outcome 'not cured or respectively dead' after 12 months (n=27, r=0.391. p=0.044) but not for *S. aureus* (Table 4, Figure 1). For all isolates from hip prostheses, there was a positive correlation between eDNA production and the patients outcome "not cured or respectively dead" after 12 months (n=21, r=0.605, and p=0.004) (Table 4).

Charlson comorbidity index (CCI) showed no correlation to eDNA production of 24 hours biofilms.

3.2. eDNA Production and Antimicrobial Susceptibility. Among 30 clinical *S. epidermidis* isolates, 16 were methicillin-resistant *Staphylococcus epidermidis* (MRSE) and 9 and 15 showed resistance to rifampicin and clindamycin, respectively. Eleven out of 30 clinical *S. epidermidis* isolates were resistant to fusidic acid. Among 30 clinical *S. aureus* isolates, 8 were methicillin-resistant *S. aureus* (MRSA) and 1 and 5 showed resistance to rifampicin and clindamycin, respectively. One out of 30 clinical *S. aureus* isolates was resistant to fusidic acid. A significantly lower eDNA production was only found in isolates resistant to fusidic acid: 4,86 for susceptible isolates versus 2,14 for resistant isolates [(eDNA 24h mean (% area), n=60, t=5.102, p<=0.001] and rifampicin: 4,76 for susceptible isolates versus 2,4 for

Table 4: eDNA production after 24 h in correlation to outcomes after 3 and 12 months with regard to bacterial species or explanted joint.

	S. aureus eDNA 24log	*S. epidermidis* eDNA 24log	Hip isolates eDNA24log	Knee isolates eDNA24log
Outcome after **3 months**	n=25	n=28	n=23	n=30
Correlation Coefficient	-0.028	-0.161	-0.293	-0.013
Sig. (2-tailed)	0.894	0.413	0.175	0.945
Outcome after **12 months**	n=21	n=27	n=21	n=27
Correlation Coefficient	-0.022	0.391	0.605	-0.018
Sig. (2-tailed)	0.923	**0.044***	**0.004****	0.928

resistant isolates [eDNA 24h mean (% area); n=60, t= 2.257, and p=0.028)].

3.3. Laboratory Parameters. The analysis of serum inflammation biomarkers revealed that all patients with *S. aureus* infections had greater mean serum levels of C-reactive protein (10.16 ± 3.33 mg/l/day; mean ± standard deviation) than patients with *S. epidermidis* infections (5.64 ± 2.14 mg/l/day) (p<0.001) during their 3 weeks clinical follow-up after surgery. Similarly mean fibrinogen levels were significantly greater in patients with PJI caused by *S. aureus* 551.46 ± 52.51mg/l^{-1}/day) than patients with PJI caused by *S. epidermidis* (457.74 (± 80.69 mg/l^{-1} /day) (p<0.001).

4. Discussion

The increasing life expectancy together with the constant progress in medicine increases the number of patients receiving medical implants, e.g., knee and hip prostheses, pacemakers, or many other medical implants and devices [19]. Therefore medical implant related infections are an increasingly substantial burden to the healthcare system [20, 21]. According to the surveillance of the European Centers for Disease Prevention and Control (ECDC) the incidence of surgical site infections (SSIs) after hip and knee surgery was 1.1%, (ranging from 0.3% to 3.8%) for THA and 0.6% (range 0.0% to 3.4%) for TKA. http://ecdc.europa.eu/en/healthtopics/Healthcare-associated_infections/surgical-site-infections/Pages/Annual-epidemiological-report-2016.aspx
In order to treat these infections a thorough understanding of the pathogenesis and the pathogens is pivotal.Clinical outcomes of PJI with respect to their causing pathogen and respective biofilm formation ability are subject of a few studies only. A prospective study in 124 patients with orthopedic implant-related osteomyelitis showed the influence of biofilm formation and antibiotic resistance on the outcome. In the subgroup of 90 patients with lower extremity infections the increase of *S. epidermidis* biofilm thickness correlated with decreased cure rates [18]. Mittag et al. examined clinical outcomes after infected knee and hip arthroplasty using clinical data of 64 patients and scores including the Western Ontario and McMaster Universities- (WOMAC-) Index, the Harris Hip Score (HHS) and the Hospital for Special Surgery Score (HSS). They did not demonstrate a correlation between implant infection classified according to the modified Tsukayama classification system [22] and outcome defined using WOMAC, HSS or HHS score [23]. However, in this study, the most frequent pathogens were *Enterococcus spp*. followed by a mixture of bacteria causing polymicrobial infections

So far a correlation between eDNA production in staphylococcal biofilms and clinical outcome of PJI has not been reported in the literature. In the present study *S. epidermidis* isolates showed significantly greater eDNA production than *S. aureus* isolates in the respective 24h biofilms [14]. Infections of *S. aureus* and *S. epidermidis* are considered distinguishable by their clinical symptoms and course: *S. aureus* infections usually present with classical local signs and symptoms of infection with pain, redness, swelling, temperature and impaired function and a systemic immune response with fever, hypotension, etc., leucocytosis and elevated C-reactive protein, etc... Infection caused by *S. epidermidis* presents usually with subacute signs and symptoms of infection and an unspecific and delayed onset. In the present patient population infections with *S. epidermidis* presented as chronic infections. Early or late acute infections were exclusively caused by *S. aureus* (Table 2).We were able to demonstrate that eDNA production of *S. epidermidis* 24 hours biofilms correlated with the clinical outcome 'not cured respectively dead' after 12 months, (p=0.044). eDNA production is a relatively stable characteristic of many *S. epidermidis* strains [14]. Thus, it may be hypothesized that production of eDNA by *S. epidermidis* isolated from PJI contributes to the pathogenesis and may be used to predict clinical outcome.

Exposure to antibiotics has been linked to eDNA production in biofilms [24, 25]. Perioperative antibiotic prophylaxis is a standard of care in orthopaedic prosthetic surgery [26]. However, Doroshenko et al. reported higher eDNA levels in biofilms of *S. epidermidis* after prior exposure to vancomycin [25]. Schilcher et al. described that subinhibitory concentrations of clindamycin increased the ability of *S. aureus* to form biofilms and shift the composition of the biofilm matrix towards higher eDNA content [27]. In the

present study, isolates resistant to rifampicin and fucidic acid produced less amounts of eDNA than susceptible ones. But, antimicrobial resistance was tested only using the disk diffusion method testing planktonic bacteria compared to biofilm susceptibility testing performed in the other studies [27] or as demonstrated by Brady and colleagues in their study comparing minimum biofilm eradication concentration and minimum inhibitory concentration breakpoint in planktonic versus biofilm grown staphylococci [28]. However, further investigation into the effects of rifampicin or fusidic acid on eDNA production should be done performing resistance testing in biofilm growth systems.

Inflammation biomarkers such as fibrinogen, C-reactive protein, and leucocyte count did not correlate with eDNA levels of 24 hours biofilms of the respective pathogens. Yet, a significant difference between the clinical presentation of PJI caused by either *S. aureus* or *S. epidermidis* was found in our patient population likewise in earlier studies [29, 30], where patients with PJI caused by *S. aureus* exhibited greater serum levels of C-reactive protein and fibrinogen compared to patients with PJI caused by *S. epidermidis*.

The limitations of the present study are inherent to the retrospective nature of the study because not all clinical and laboratory data are available, and there is a rather small sample size of a nevertheless very well defined patient population. Due to the small sample size, multivariate statistical analysis was not indicated. Moreover, in vitro conditions of biofilm formation may not fully reflect clinical biofilms in PJI [31].

5. Conclusion

In conclusion, a correlation between increased eDNA production of *S. epidermidis* 24h biofilms and adverse clinical outcome after 12 months was demonstrated. Quantification of eDNA production of the pathogen as a surrogate marker for biofilm formation might be a potential predictive marker for the management of PJI caused by *S. epidermidis*. eDNA might also be a possible therapeutic target. Further prospective and sufficiently powered clinical studies will be needed to strengthen the role of eDNA production of pathogens on the clinical course and its relevance in PJI.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Beata Zatorska designed the study, performed the analyses, collected the data, and drafted the paper. *Nicolas Haffner* assisted in data collection, study design, and data interpretation. *Carla Renata Arciola* contributed substantially to the scientific background of the paper and writing the discussion. *Luigi Segagni Lusignani* assisted in the statistical data analyses. *Elisabeth Presterl* assisted in data collection and study design and reviewed the manuscript critically. *Magda Diab Elschahawi* contributed substantially to the concept, research design, and writing the paper. All authors have read and approved the final manuscript.

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Supplementary Materials

Supplementary material contains detailed data of the eDNA production after 6 and 24 hours in biofilms of bacterial isolates from hip and knee joint after explantation. The measurements were done using CLSM and TOTO1 staining. Table S1: eDNA production (mean % area eDNA) after 6 and 24 hours in biofilms of hip and knee joint explants irrespective of staphylococcal species. *(Supplementary Materials)*

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Research Article

Comparison of Elution Characteristics and Compressive Strength of Biantibiotic-Loaded PMMA Bone Cement for Spacers: Copal® Spacem with Gentamicin and Vancomycin versus Palacos® R+G with Vancomycin

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Purpose. Copal® spacem is a new PMMA bone cement for fabricating spacers. This study compares elution of gentamicin, elution of vancomycin, and compressive strength of Copal® spacem and of Palacos® R+G at different vancomycin loadings in the powder of the cements. We hypothesized that antibiotic elution of Copal® spacem is superior at comparable compressive strength. *Methods*. Compression test specimens were fabricated using Copal® spacem manually loaded with 0.5 g gentamicin and additionally 2 g, 4 g, and 6 g of vancomycin per 40 g of cement powder (COP specimens) and using 0.5 g gentamicin premixed Palacos® R+G manually loaded with 2 g, 4 g, and 6 g of vancomycin per 40 g of cement powder (PAL specimens). These specimens were used for determination of gentamicin and vancomycin elution (in fetal calf serum, at 22°C) and for determination of compressive strength both prior and following the elution tests. *Results*. Cumulative gentamicin concentrations ($p < 0.005$) and gentamicin concentration after 28 days ($p \leq 0.043$) were significantly lower for COP specimens compared to PAL specimens. Cumulative vancomycin concentrations were significantly higher ($p \leq 0.043$) for COP specimens after the second day. Vancomycin concentrations after 28 days were not significantly higher for the Copal specimens loaded with 2 g and 4 g of vancomycin. Compressive strength was not significantly different between COP specimens and PAL specimens before elution tests. Compressive strength after the elution tests was significantly lower ($p = 0.005$) for COP specimens loaded with 2 g of vancomycin. *Conclusion*. We could not demonstrate consistent superior antibiotic elution from Copal® spacem compared to Palacos® R+G for fabricating gentamicin and vancomycin loaded spacers. The results do not favor Copal® spacem over Palacos® R+G for the use as a gentamicin and vancomycin biantibiotic-loaded spacer.

1. Introduction

Antibiotic-loaded bone cements are used to fabricate spacers during two-stage exchange of knee and hip prostheses for the treatment of periprosthetic joint infection (PJI) [1]. During stage-one operation, the infected prosthesis is removed and a poly(methyl methacrylate) (PMMA) bone cement spacer is temporarily implanted. The spacer works as a drug delivery system for antibiotics in order to achieve high local concentrations [2]. Additionally, it stabilizes the joint during mobilization and prevents soft tissue contraction [3]. Antibiotic loading of the bone cement can be performed right before the mixing procedure (manually loaded) or during the industrial production of the powder component (premixed).

Table 1: Compositions of powder of the prepared specimen groups.

Specimen group	Active gentamicin amount in g	Active vancomycin amount in g
Pal2	0.5	2.0
Pal4	0.5	4.0
Pal6	0.5	6.0
Cop2	0.5	2.0
Cop4	0.5	4.0
Cop6	0.5	6.0

The spacer is molded after initiation of the polymerization of the cement by mixing its powder and liquid.

To date, some bone cement brands that are intended for the use for fixation of total joint replacements are also used to fabricate spacers, one example being Palacos® R+G [4, 5]. At the same time, cement modifications with improved antibiotic elution are tested [6]. Recently, a bone cement brand, designed specifically for fabricating spacers (Copal® spacem), was launched. The powder of this brand includes calcium carbonate particles, which serve as both contrast agent and biodegradable porogen. Antibiotics are not premixed into Copal® spacem, with the intention that an appropriate amount of pathogen-adjusted antibiotic will be mixed with the powder of the cement just before spacer fabrication and implantation. Bitsch et al. reported improved antibiotic elution characteristics of Copal® spacem when a single antibiotic was added [7]. *In vitro* testing has shown that combination of antibiotics in a spacer can induce synergistic antibiotic elution [2] and superior antibacterial effects [8–10]. The combination of gentamicin and vancomycin ensures effective action against a broad range of PJI-causing pathogens [11]. Thus, there are reports of clinical use of spacers fabricated using manual loading of the gentamicin premixed powder of Palacos® R+G with vancomycin [1, 4].

In the present study, we compared antibiotic elution and compressive strength of Copal® spacem when gentamicin and vancomycin were added (COP specimens) to those properties for Palacos® R+G when vancomycin was added (PAL specimens). For COP, the amount of gentamicin added is the same as it is premixed in Palacos® R+G. For both cements, the antibiotic(s) were added to the powder using manual mixing. The investigation involved determination of the influence of vancomycin loading on the aforementioned cement properties and the compression tests were run both prior to and following the end of the elution tests. We hypothesized that gentamicin and vancomycin elution from COP specimens are significantly higher than from PAL specimens at comparable compressive strengths.

2. Materials and Methods

2.1. Specimen Preparation. Palacos® R+G (Heraeus Medical GMBH, Germany) contains premixed 0.8 g gentamicin sulphate (0.5 g active gentamicin). To produce equal gentamicin loading, 0.84 g gentamicin sulphate (0.5 g active gentamicin) (Caelo, Germany) was added to the powder of Copal® spacem (40 g) (Heraeus Medical GMBH, Germany). Then 2.05 g, 4.10 g, and 6.15 g vancomycin hydrochloride (Hikma Farmaceutica, Portugal) were added to the powder of Copal® spacem. The same amounts of vancomycin hydrochloride were added to the powder of Palacos® R+G. Thus, 6 cement formulations were used (Table 1).

Manual loading was performed following the recommendations by Kuhn et al. The antibiotics were thoroughly ground in a mortar and then the cement powder was successively added while stirring [4]. After that, the mixture was combined with the liquid of the cement, to produce a dough which then was poured into a mold to yield short, cylindrical specimens (diameter and height = 6 mm and 12 mm, respectively). These specimens were used for both the elution and the compression tests.

2.2. Elution Tests. The specimen was immersed in 1.5 ml fetal calf serum (FCS), in ambient laboratory conditions (temperature = 22 ± 1°C) for four weeks. FCS was exchanged every 24 hours. Samples of the eluate were taken every 24 hours for the first 7 days as well as after 14 and 28 days and stored at -20°C for determination of antibiotic concentration. Vancomycin concentrations were measured in a clinical analyzer (Hitachi Analyzer, Roche, Germany) with a homogene enzyme immunoassay (Online TDM Vancomycin Cobas, Roche (upper limit of measurement 50.0 μg/ml and lower limit of measurement 5.0 μg/ml with coefficient of variance 1.1%–4.9%)). Gentamicin concentrations were measured in the same way with the CEDIA® Gentamicin II Assay (Microgenics, Germany (upper limit of measurement 12.0 μg/ml and lower limit of measurement 0.00 μg/ml with coefficient of variance 3.0–6.2% for gentamicin)). If the concentration exceeded the upper limit of measurement, the eluate was diluted with FCS, the measurement was repeated, and the true concentration was calculated. For each of the formulations, 6 specimens were tested.

2.3. Compression Tests. The tests were conducted in accordance with the ISO 5883 [12] using a servohydraulic material testing machine (Z020, Zwick/Roell, Ulm, Germany), at a crosshead displacement of 10 mm/min. Tests were performed on two sets of specimens, prior to (n = 5) and immediately following the end of the elution test (n = 5).

2.4. Statistical Analysis. Results are presented as mean and 95% confidence intervals. The Kolmogorov-Smirnov-test was used to determine normal distribution of variables. Levene's

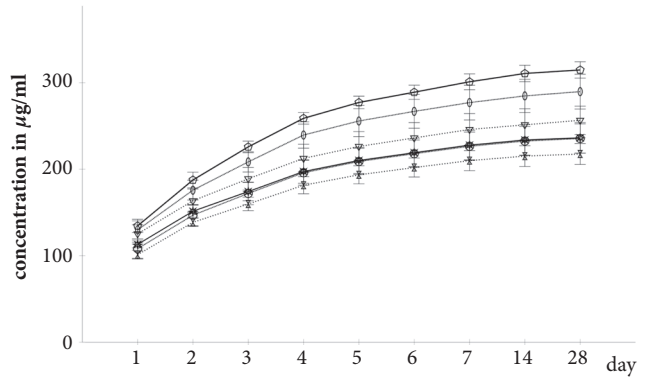

Figure 1: *Cumulative gentamicin concentrations in FCS sorted by specimen group*. Continuous line: vancomycin amount 6g; dotted line: vancomycin amount 4g; far dotted line: vancomycin amount 2g; asterisks: Cop6; pentagons: Pal6; circles: Cop4; ellipses: Pal4; double triangles: Cop2; triangles: Pal2; whiskers: 95% confidence intervals.

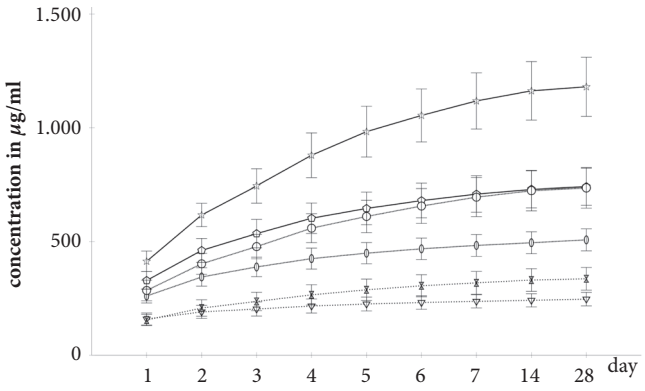

Figure 2: *Cumulative vancomycin concentrations in FCS sorted by specimen group*. Continuous line: vancomycin amount 6g; dotted line: vancomycin amount 4g; far dotted line: vancomycin amount 2g; asterisks: Cop6; pentagons: Pal6; circles: Cop4; ellipses: Pal4; double triangles: Cop2; triangles: Pal2; whiskers: 95% confidence intervals.

test was used to test for equality of variances. T-tests for independent values were performed to identify significant differences in means. Significance was indicated if $p < 0.05$. All of these tests were performed using a commercially-available software package SPSS 24.0 (SPSS Inc., USA).

3. Results

The COP specimens produced significantly lower cumulative gentamicin concentrations than the PAL specimens at each of the 9 time points ($p \leq 0.005$) (Figure 1).

The Cop2 specimens produced significantly higher ($p \leq 0.043$) cumulative vancomycin concentrations after day 2. For the Cop4 specimens significantly higher ($p \leq 0.035$) cumulative vancomycin concentrations were measured after day 1 and for the Cop6 specimens at every measurement ($p \leq 0.004$). Figure 2 depicts the cumulative vancomycin concentrations

Long term elution is crucial for the treatment with spacers. Table 2 depicts the determined antibiotic concentrations after 28 days.

Compressive strengths before elution tests were below the ISO 5883 recommended 70 MPa threshold, except for Pal4 (Table 3).

After the elution tests, the compressive strength of Cop2 was significantly lower ($p = 0.005$) than of Pal2. The compressive strength of the COP and the PAL specimens loaded with 4 g and 6 g of vancomycin underwent significant reduction ($p \leq 0.014$) during antibiotic elution.

4. Discussion

Antibiotic-loaded PMMA bone cements are used as spacers to provide high local antibiotic concentrations and mechanical stability of the affected joint after removal of the infected prosthesis [2]. The bone cement Copal® spacem was recently introduced as a cement designed specifically for high antibiotic elution. However, data on antibiotic elution and mechanical properties of the Copal® spacem cement are lacking. The current study compared antibiotic elution and compressive strength of Copal® spacem and of Palacos® R+G as biantibiotic cements loaded with gentamicin and vancomycin.

For these biantibiotic formulations, we found lower gentamicin elution of the manually blended Copal® spacem compared to the gentamicin premixed Palacos® R+G. In contrast, Bitsch et al. found superior cumulative antibiotic elution from Copal® spacem in comparison to Palacos® R, when both these cements were manually monoantibiotic-loaded with gentamicin. In their study, vancomycin release displayed a slope of the cumulative antibiotic concentrations, which leveled earlier with decreasing amount of added vancomycin [7]. In accordance with these results, we found significant higher cumulative elutions but not higher vancomycin concentrations after 28 days for Cop2 and Cop4.

In the current investigation, manually gentamicin and vancomycin loaded Copal® spacem was compared to commercially available gentamicin premixed Palacos® R+G manually blended with vancomycin. Elution of Copal® spacem is enhanced by addition of calcium carbonate as a soluble porogen [7]. Such porogens enhance antibiotic elution by pore formation [6]. Although controversially discussed [13–15], premixed antibiotics are reported to be better eluted than manually loaded antibiotics [8, 16]. Ferraris et al. found larger inhibition zones around Palacos® R+G specimens compared to manually gentamicin loaded Palacos® R specimens, indicating higher antibiotic elution [8]. Comparable results were presented in the study by Lewis et al. demonstrating higher antibiotic elution from industrial loaded cements compared to manually loaded cements [17]. Thus, the elution enhancing effect of calcium carbonate in Copal® spacem did not compensate for the weaker elution of the manually loaded gentamicin compared to the premixed gentamicin. For the manually loaded vancomycin, the elution enhancing effect of calcium carbonate in Copal® spacem leads to higher cumulative antibiotic elution by increasing the initial burst

Table 2: Comparison of determined antibiotic concentrations after 28 days sorted by specimen group and measured antibiotic.

Specimen group by amount of added vancomycin in g	Measured antibiotic	Antibiotic concentration for COP mean in μg/ml (CI 95%)	Antibiotic concentration for PAL mean in μg/ml (CI95%)	p
2	Gentamicin	2.46 (2.03 – 2.91)	5.21 (2.62 – 7.80)	*0.041*
4	Gentamicin	2.97 (2.35 – 3.59)	4.93 (3.84 – 6.03)	*0.002*
6	Gentamicin	2.53 (2.02 – 3.03)	4.08 (2.43 – 5.73)	*0.043*
2	Vancomycin	5.52 (5.01 – 6.02)	5.52 (3.45 – 7.59)	1.000
4	Vancomycin	12.03 (11.19 – 12.88)	12.82 (6.80 – 18.84)	0.754
6	Vancomycin	17.73 (15.92 – 19.55)	11.45 (8.41 – 14.49)	*0.001*

Table 3: Comparison of compressive strengths before and after elution tests sorted by specimen group.

Specimen group	Compressive strength before elution mean MPa (95% CI)	Comparison of groups		Compressive strength after elution mean MPa (95% CI)	before vs. after elution p
		before elution tests p	after elution tests p		
Pal2	69.4 (66.8 – 72.0)	0.193	*0.005*	70.4 (67.3 – 73.2)	0.486
Cop2	66.9 (62.6 – 71.1)			63.9 (60.1 – 67.7)	0.173
Pal4	70.7 (65.5 – 76.0)	0.637	0.805	59.8 (57.5 – 62.1)	*0.001*
Cop4	69.5 (64.6 – 74.4)			60.1 (57.0 – 63.2)	*0.002*
Pal6	67.7 (58.2 – 77.1)	0.461	0.279	57.7 (53.8 – 61.6)	*0.014*
Cop6	65.1 (62.5 – 67.7)			55.5 (52.1 – 59.0)	*< 0.000*

release of vancomycin. However, high initial vancomycin elution goes along with enhanced vancomycin depletion. Consequently, the effect of improved vancomycin release by Copal® spacem fades by time in dependence of the amount of added antibiotic.

Compressive strength was reduced irrespectively of the amount of added antibiotic without significant differences between the COP and the PAL groups before the elution tests. After the elution tests, reduction of compressive strength was caused by void and crack formation due to antibiotic elution of the manually loaded antibiotics [18]. Beyond a critical antibiotic concentration, antibiotic elution leads to the development of a mechanically relevant percolation network causing significant reduction of compressive strength [16]. In our study, the specimens of both groups with 4 g and 6 g of vancomycin exceeded this critical antibiotic concentration. However, although the absolute amounts of antibiotics in the cement powders were the same for the corresponding groups, COP specimens had a higher proportion of manually added antibiotic than PAL specimens. The difference in compressive strength of the 2 g vancomycin groups shows that the critical antibiotic concentration of the manually added antibiotics for mechanically relevant percolation lies between Cop2 and Pal2.

The current study has a number of limitations. We examined antibiotic release by determination of concentrations, which does not allow conclusion on antimicrobial activity. Thus, we cannot state whether the higher antibiotic burst release of vancomycin from COP specimens is of advantage compared to the concentrations produced by PAL specimens. All measured concentrations exceeded the minimal inhibitory concentration of the most common pathogens for PJI, even after 28 days [19, 20]. After this time, antibiotic measurements were stopped, because concentrations fell below the lower limit of measurement for vancomycin. In contrast to antimicrobial testing, determination of concentrations was chosen for better comparability and the measurement method for its very low coefficient of variance. Furthermore, our study was limited to the antibiotics gentamicin and vancomycin. Other combinations need to be investigated, but the chosen combination is in clinical use [1, 4]. Finally, Copal® spacem has shown better wear behavior compared to Palacos® R *in vitro* [7]. This could reduce wear particle induced osteolysis, when used to fabricate articulating spacers. Copal® spacem might be advantageous for the treatment of PJI with a known pathogen as monoantibiotic-loaded spacer. However, if the pathogen is unknown, a biantibiotic-loaded spacer with vancomycin covering a broad spectrum of gram-positive and gentamicin covering a broad spectrum of gram-negative pathogens is warranted [11]. Our results are specifically relevant for this indication. For neither Copal® spacem nor Palacos® R+G, the addition of 4 g and 6 g of vancomycin can be recommended due to mechanical considerations [2, 21–23]. For the addition of 2 g of vancomycin, we found a higher initial burst release of vancomycin, but no significant difference of concentrations after 28 days. Additionally, significantly lower gentamicin concentrations were determined for Copal® spacem throughout the study. Based on these *in vitro* results, Copal® spacem is not of advantage for the use as a gentamicin and vancomycin biantibiotic-loaded, static spacer in comparison to Palacos® R+G.

5. Conclusion

Copal® spacem demonstrated inferior gentamicin elution. Cumulative vancomycin elution was significantly higher for

all COP specimens, whereas vancomycin concentrations after 28 days showed no relevant differences. We could not demonstrate consistent superior antibiotic elution from Copal® spacem in comparison to Palacos® R+G as a biantibiotic gentamicin and vancomycin loaded cement. Thus, our results do not favor Copal® spacem over Palacos® R+G for gentamicin and vancomycin biantibiotic-loaded spacers.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Outcome of Irrigation and Debridement after Failed Two-Stage Reimplantation for Periprosthetic Joint Infection

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Introduction. Two-stage revision is the gold standard for the treatment of deep implant infection after knee or hip arthroplasty. Irrigation and debridement may be a treatment option for failed 2-stage revisions in cases where a reinfection occurs within 30 days or the symptoms exist not longer than 3 weeks and is appealing because of its low morbidity. We determined the incidence of recurrent infections following irrigation and debridement for failed two-stage revision hip and knee arthroplasty. *Methods*. We performed a single center retrospective review of periprosthetic hip and knee infections treated with a two-stage procedure from 2002 to 2010. All patients that subsequently underwent irrigation and debridement for a subsequent infection were selected for the current study. *Results*. 440 two-stage revisions were performed between 2002 and 2010. Fifty-one two-stage revisions failed (11.6%). Nineteen failed two-stage revisions were treated with irrigation and debridement; 12 (63.2%) patients remained free of infection at follow-up (mean follow-up: 39 months; range, 24-90 months), infection persisted in 6 patients (31.6%), and 1 patient died (5.3%). *Conclusions*. Success rates of irrigation and debridement for failed two-stage procedures are similar to the success rates of irrigation and debridement in primary implant infections. According to the current paper, irrigation and debridement are an acceptable treatment for acute reinfections after failed two-stage revision if performed within the first 30 postoperative days after failed two-stage procedure or if symptoms are present for less than 3 weeks in the presence of a susceptible organism.

1. Introduction

Periprosthetic infection after total joint replacement is a devastating complication and occurs in up to 2% of primary joint replacements [1–5]. Treatment options include irrigation and debridement (I&D) with component retention [6–10], one-stage revision [11–13], or two-stage revision utilizing an antibiotic containing cement spacer [14–16].

Two-stage revision remains the golden standard treatment in the United States with infection-free survival rates of 80-100% [17–19]. An antibiotic containing cement spacer [14, 16] and intravenous antibiotics are routinely used for two-stage procedures. Zimmerli et al. [20] recommended two-stage revisions for patients with symptoms for more than 3 weeks or an index procedure performed more than 30 days ago.

Patients presenting with symptoms for less than 3 weeks or within 30 days of primary joint replacement without a sinus tract or radiographic evidence of component loosening can be considered for an I&D with retention of components in case of and a susceptible organism [21]. This approach is attractive because of its low-morbidity and cost effectiveness. However, failure rate of 7-79% has been reported and I&D is therefore in general considered less effective than two stage revision [6, 22].

There are much less clear recommendations for the treatment of recurrent infection following two stage revisions. Whiteside et al. [23] reported control of infection in 17 of 18 patients using aggressive I&D and intraarticular antibiotic infusion over 6 weeks after a failed two-stage treatment attempt.

The aim of the current study was to evaluate the clinical success rates of I&D after failed two-stage revision and to investigate the impact of the type of organism, patient age, general health condition (ASA), and comorbidities on treatment outcome.

2. Materials and Methods

The current study is a retrospective chart review of 440 two-stage revisions for periprosthetic knee or hip infection performed at one tertiary referral center between 2002 and 2010.

Patient demographics including age, gender, BMI, health status (ASA), the timespan between I&D, and the prior failed two-stage procedure, as well as number and type of prior surgeries, were recorded. The American Society of Anesthesiologists (ASA) physical status classification score was used as a proxy variable for health status. The types of organisms and sensitivities were documented for all procedures. Quinolone resistant Gram-negative bacteria, rifampicin-resistant Staphylococcus, Enterococcus, and Candida were classified as "difficult to treat" (DTT) in accordance of Winkler et al. [27].

The diagnosis of infection prior to the index two-stage procedure was based on clinical signs, blood work (ESR, CRP), positive synovial fluid aspiration, and intraoperative cultures (following the state of art [28]). The index two-stage revisions included removal of implants and bone cement (Stage I). All patients received a static antibiotic containing cement spacer (knees) or an articulating spacer (hip) as well as systemic antibiotics based on organism sensitivity for 2 weeks intravenously and for an additional 4 weeks orally. The articulating hip spacers were performed as mould-spacers with an endoskeleton (67%) or as handmade spacers (33%) [29]. The knee spacers were performed as static, handmade spacers with an endoskeleton [30]. Two weeks after stopping the systemic antibiotics successful eradication was confirmed by repeat joint aspiration. If the aspiration was negative, CRP remained less than 2 g/dL and there was no sinus tract and a new implant was inserted (Stage II).

Reinfection occurred in 51 patients (11.6%) of 440 two-stage revisions. If a reinfection occurred (diagnosis of reinfection followed the consensus criteria by Zmistowski et al. [1]) within 30 days after two-stage revision or patients presented with an acute reinfection (symptoms for less than 3 weeks), aggressive, if necessary repeated I&D was performed. Nineteen of 51 patients fulfilled the inclusion criteria (32 patients were treated with a second two-stage procedure). The mean age at I&D after failed two-stage procedure was 67.3 years (range, 45.2 – 84.5 years); there were 12 male and 7 female patients, 12 hips and 7 knees, 10 left and 9 right joints; the mean BMI was 29.6 kg/m^2 (range, 21.5 to 36.4 kg/m^2). Mean follow-up was 39 months (range, 24-90 months). At the time of each follow-up the absence of infection was evaluated by clinical criteria (no sinus tract, no swelling, no erythema, and no tenderness); if there was a reasonable suspicion of recurrent infection, an immediate work-up was done adhering to the guidelines by Parvizi et al. [28].

I&D was performed utilizing the preexisting incisions. After a thorough synovectomy and irrigation of the surgical site all removable components (hip: head and liner; knee: articular insert) were removed. Now the implant was cleaned and a through irrigation utilizing a minimum of 10 L of antiinfectious irrigation was performed. Finally the surgical field was covered with new drapes, new instruments were opened, and the surgeons and assistance were regloved and regowned. New mobile components were put in place and the wound was closed in layers in a usual way. If the soft tissues were not stable enough, 1-3 polyurethane sponges were inserted under the fascia or subcutaneously and were connected to a vacuum producing devise via tubes [31]; afterwards the wounds were still closed in layers under meticulous reconstruction and accurate adaptation of the tissue layers. A repeated I&D was performed 3-6 days later in a technique described by Kelm et al. [31]. The indication for a repetition of I&D was evidence of persistent microorganism intraoperatively, persisting drainage, no decrease of C-reactive protein within 6 days combined with clinical signs of persistent infection (overheat, reddening), or persisting sepsis.

All patients terminated the use of antibiotics two weeks after last surgery ("postoperative antibiotics", Tables 2 and 4), and no suppression therapy was used.

Failure was defined as any additional surgery due to infection after hospital discharge. Only patients with a minimum follow-up of 24 months were included in the current study.

Descriptive statistics were calculated, including mean and frequency. Mann–Whitney test was used to determine differences between successes and failures. Chi-square tests were used to determine differences in proportions between dichotomous data.

All statistical analyses were performed using IBM SPSS Statistics software version 23 (Armonk, NY: IBM Corp.). A p-value of less than 0.05 was considered to be statistically significant.

3. Results

Of 19 patients who underwent I&D for failed two-stage revision, 12 (63.2%) patients were infection-free after a minimum follow-up of 24 months (mean 39 months, range 24-90 months). A recurrent deep infection occurred in 6 patients (31.6%) and one patient died (5.3%). 8/11 hips (72.7%) and 4/7 (57.1%) knees were infection-free after the minimum follow-up.

Patients with successful (Tables 1 and 2) and failed treatment (Tables 3 and 4) differed in regard to BMI (median, success group 31.5 kg/m^2, reinfection group 25.5 kg/m^2, $p = 0.026$), but there were no differences in age ($p = 0.892$), ASA grade ($p = 0.989$), and number of I&Ds ($p = 0.243$).

Causative organisms cultured at the time of I&D are reported in Tables 2 and 4. "Difficult to treat" organisms occurred in 6 cases. Two polymicrobial infections were observed. No statistically significant difference was found concerning the distribution of DTT-organisms or polymicrobial infections between the successfully treated and failed group.

4. Discussion

Periprosthetic infections are a devastating complication. Treatment options range from two-stage revision [22], one-stage exchange [11], or irrigation and debridement with retention of components [8]. There is an ongoing debate about the most appropriate treatment of an acute implant infection.

Table 1: Successful cases and demographics.

Patient	Age (years)	Gender	Joint	Side	ASA grade	Follow up (months)	BMI	Comorbidities
1	73.5	male	Hip	R	3	33	34.2	HTN, A
2	46.5	male	Hip	R	3	34	32.1	HTN, SM, A
3	68.3	male	Hip	L	3	28	30.9	HTN, CKF
7	74.4	female	Hip	L	3	63	36.4	HTN, post enterovesical fistula
8	63.2	male	Hip	L	2	77	21.5	SM, DM
9	64.3	female	Hip	R	2	24	35.4	HTN, CHF
11	52.9	female	Hip	L	2	90	34.3	-
12	75.9	female	Knee	R	3	24	32.8	HTN, absolute arrhythmia in atrial fibrillation
13	45.2	male	Knee	R	2	25	29.3	Post ORIF femur
14	76.2	male	Knee	R	3	30	29.8	HTN, CHD, CHF, CKF, absolute arrhythmia in atrial fibrillation
18	84.5	male	Hip	L	4	28	24.2	HTN, CHD, CKD, post apoplexy, morbus parkinson, chronic cystitis
19	67.4	female	Knee	R	3	27	29.7	Bipolar psychosis, lumbar spinal syndrome

DM = diabetes mellitus, HTN = arterial hypertension, CHD = coronary heart disease, CHF = chronic heart failure, CKF = chronic kidney failure, COPD = chronic obstructive pulmonary disease, SM = smoker, A = alcohol (> 20 g/d), DA = drug abuse

While eradication rates are higher in two-stage procedures, quality of life and postoperative function might be better after one-stage and I&D procedures, respectively [32–34].

Eradication rates following revision of primary implant infections range from 61 to 100% for different treatment protocols [25, 32, 33]. However, literature on the treatment of recurrent infection is scarce. The current study reports the eradication rate utilizing I&D for recurrent periprosthetic infection within a time-window of 30 days or occurring symptoms less than 3 weeks in patients with failed two-stage revision for periprosthetic infection. In the present study similar eradication rates for an I&D (63.2%) after failed two-stage revision were shown compared to I&D in primary deep implant infection [6, 35, 36].

The current study has the following limitations. First, this is a retrospective study. Second, while the report is based on a large group of patients undergoing two-stage revision surgery cases, numbers in the current group of I&D for recurrent infection are too small to analyze the impact of the type of organism and its sensitivity on overall outcome of I&D. The numbers are also too small to make a differentiated analysis between hips and knees. Third, since patients did not undergo laboratory screening or recurrent aspiration, infections were assumed to be eradicated based on clinical criteria exclusively. Finally, the use of a polyurethane sponge with a vacuum-producing device during repeated I&Ds is not very well described in the literature. There are some reports using V.A.C-Instill with small patient-numbers, but only one study, in which also a deep sponge was placed and the wound was still closed anatomically [31] as in the current study. In our center the use of sponges with a vacuum system was left after 2010.

There are only a few papers that report on the treatment of failed treatment attempts of deep implant infections. There is no common sense of the best treatment after failed two-stage procedure. Stammers et al. [24] reported failure rates of 42% (8/19 knees) (Table 5) for repeat two stage revision after failed initial two stage treatment.

There is a study using a decision tree analysis to determine the best treatment (quality of life) after failed revision for deep implant infection. Wu et al. [37] expected the highest QoL utilizing arthrodesis following a failed two-stage revision in patients with total knee replacement. In a clinical review Sherrell et al. [25] reported failure rates of 34% in two-stage revisions for patients who underwent I&D followed by two-stage revision due to persisting infection. The authors assumed that the failure rate of 34% is higher than in patients who undergo two-stage revision only (Table 5).

Pagnano et al. [26] reported a reinfection rate of 18.7% (27/144 hips) after a first two-stage revision due to periprosthetic infection. The authors reported four treatment options after failed first two-stage revision: antibiotic suppression therapy, I&D, resection arthroplasty, or a second two-stage revision. Two of 3 patients did not need any further surgery after I&D and continuous oral suppressive antibiotic therapy. Sixteen patients were treated by resection arthroplasty after failed two-stage procedure. Three of these 16 patients (18.8%) had to undergo further surgeries for recurrence of infection. Eleven patients underwent a second two-stage revision, in 8 patients (72.7%), a recurrence of infection occurred and further surgeries were needed (Table 5).

In the current study, if necessary, repeat I&D was performed (range, 1-10). Kelm et al. [31] reported an eradication rate of 92.9% using the above mentioned protocol. However,

Table 2: Successful cases with organism type, resistogram, and antibiotics; failed two-stage revision was done at a tertiary referral center; prior surgeries (column 2) were done in external clinics.

Patient	Revision surgeries prior to failed two-stage revision	Organism type: failed two-stage revision	Antibiotics preoperative	Number of surgeries (I&D)	Organism type: I&D	Antibiotics postoperativ	Resistant against
1	Two-stage revision	MRSE	Va, Ti, Ri	1	MRSE	Va, Ti, Ri	Ox, Ri, Ci, Ge, Cl, Im
2	-	MRSE	Le, Ri	7	MRSE	Le, Va, Ri	Ox, Ci, Ge, Cl
3	Revision due to bursitis intertrochanterica	Staph. capitis	Le, Ri	1	Strepto. intermedius	Le, Ri	Cl
7	-	Staph. aureus	-	8	Staph. aureus	Le, Fl, Ri	-
8	Bursectomy, Exchange of cup		Le, Ri	7	MRSE	Va, Cl, Ri	Ox, Ce, Im
9	Soft tissue revision	Strepto. agalactiae	Fl, Ri	1	Enterococcus faecalis	Fl, Am, Ri	Ge, Cl, Ce
11	-		Le, Ri	2	Staph. aureus	Le, Ri	-
12	Two-stage revision		Le, Ri	5	(1) Enterococcus faecalis (2) Peptostrepto. magnus	Le, Amp, Ri	(1) Ge, Cl (2) -
13	ORIF (tibiaplateau fracture)	MRSE	-	6	Escherichia coli	Le, Ce, Ri	-
14	-	Staph. epi	Le, Ri	11	MRSE	Va, Ri	Ox, Ge, Cl, Ce, Va, Im
18	Two-stage revision	Staph. aureus	-	7	Escherichia coli	Me, Ri	Le, Ci,
19	3x two-stage revision	Strept. simulans	Le, Ri	5	Escherichia coli	Le, Ri	-

MRSE = methicillin-resistant staphylococcus epidermidis, Ox = oxacillin, Ri = rifampicin, Le = levofloxacin, Ci = ciprofloxacin, To = tobramycin, Fl = flucloxacillin, Ge = gentamicin, Cl = clindamycin, Ce = cefuroxime, Va, = vancomycin, Li = linezolid, Im = imipenem, Ti = tigecycline, Am = amoxicillin, Amp = ampicillin, Mo = moxifloxacin, Me = meropenem

Table 3: Failed cases and demographics.

Patient	Age (years)	Gender	Joint	Side	ASA grade	Follow up (months)	BMI	Comorbidities
5	76.6	female	Hip	R	3	55	23.5	Post cerebellar infarction, osteoporosis, post humerus-fracture
6	70.8	male	Hip	L	3	29	27.8	DM, HTN, CHD, CHF, CKF, post quadruple coronary artery bypass, both sided carotid artery stenosis
10	62.4	male	Hip	R	2	29	26.3	SM, A, post transient ischemic attack
15	61.9	male	Knee	L	2	49	29.8	HTN, post phlebothrombosis
16	78.5	female	Knee	L	3	35	23.5	-
17	62.1	male	Knee	L	4	24	24.7	DM, HTN, CHD (bio heart valve, pacemaker), CKD (IgA nephropathy), A, post phlebothrombosis

DM = diabetes mellitus, HTN = arterial hypertension, CHD = coronary heart disease, CHF = chronic heart failure, CKF = chronic kidney failure, COPD = chronic obstructive pulmonary disease, SM = smoker, A = alcohol (> 20 g/d), DA = drug abuse

the literature is inconsistent and some studies [38–40] report a higher failure rate with repeated I&Ds.

In the current study Staphylococcus was the predominant bacterium (52.6%; coagulase-negative staphylococci 42.1%, Staphylococcus aureus 10.5%). This finding is in line with current literature [41, 42]. "Difficult to treat"-organisms (DTT) occurred in 6 patients. Winkler et al. [27] described rifampicin-resistant Staphylococci (Patient 1), quinolone-resistant gram-negative bacteria (Patient 18), Enterococci (Patient 5, 9, 12 and perished patient), and Candida as DTT-organisms. No differences concerning the success of I&D were observed in the present study according to the presence or absence of DTT-organisms. One polymicrobial infection (Patient 5 and 12) occurred in each group. It is not clarified yet if the classification of DTT-infections should include polymicrobial infections. Only 3 patients showed the same organism at the time of two-stage revision and I&D (2x MRSE: Patient 1 and 2; 1x Staph. aureus: Patient 7). Two patients (Patient 14 and 15) developed methicillin-resistance (Staph. Epidermidis). Zmistowski et al. [43] differentiate between recurrence of infection (same organism at the failed two-stage procedure and at the renewed flare-up infection) and "new" reinfection with a change of microorganism. They showed a persistent infection with the same organism in 31.5%. Haddad et al. [42] also reported a change of organism in reinfection in 3 of 4 (75%) patients and specified these patients as reinfected compared to the fourth patient with a "persisting infection". Kraay et al. [44] actually described a 100% "new" infection-rate after failed two-stage procedure (28 patients). Triantafyllopoulos et al. [45] also showed more "new" infections than persistent infections with the same microorganism. In the current study 84.2% of patients showed "new" infection. Due to the majority of "new" infections it can be concluded, as Zmistowski et al. [43] and Triantafyllopoulos et al. [45] do, that the host status with all possible comorbidities may be a major factor. The control and improvement of comorbidities cannot be overstated as the mentioned studies describe a high vulnerability of the host for a "new" infection with a high Charlson Comorbidity Index. For patients with a high Charlson Comorbidity Index as a vulnerable host and an increased risk of perioperative complications the concept of I&D (defined as an acute reinfection within above mentioned time window) is a feasible option of treatment. On the other hand Zmistowski et al. [43] showed the only independent predictor of persistent periprosthetic joint infection was a primary infection with Staphylococcus in general, and MRSA in particular. These numbers can be shown in the current study as well as all three persistent infections occurred in patients with a Staphylococcus-infection. At the current study all persistent infections (n = 3; same microorganism within the failed two-stage procedure and the reinfection) are in the "infection free" group after I&D. It is unclear why the success rate in persistent infections was 100%. Three reasons of this circumstance could be as follows: first, the basis of the mature biofilm (prosthesis) was removed during the two-stage procedure and it might be that the revival of a mature biofilm at the new prosthesis was sufficiently stopped by a timely I&D. Second, the numbers of patients are too small. Third, the follow-up period is too short. The antibiotic therapy used in the current study follows the guidelines by Osmon et al. [20].

In summary, the failure rate of I&D for acute recurrence of infection (within 30 days of symptoms or 3 weeks of two stage procedure) following failed two-stage treatment was 31.6% in the present study. Therefore the concept of I&D after failed two-stage procedure might be an option in acute reinfections more than in persistent infections. The success rate is comparable to I&D for infection of a primary joint replacement. Careful indication (see criteria), meticulous surgical debridement, and close cooperation between the microbiologist, infectious disease doctor, and surgeon are recommended.

Table 4: Failed cases.

Patient	Revision surgeries prior to failed two-stage revision	Organism type: failed two-stage revision	Antibiotics preoperative	Number of surgeries (I&D)	Organism type: I&D	Antibiotics postoperative	Resistant against
5	Inlay exchange (multiple dislocations), multiple surgeries due to infection	(1) Staph. aureus (2) Staph. haemolyticus	Le, Ri	5	(1) MRSE (2) Enterococcus faecium	Va, Ri	(1) Ox, Ci, Cl (2) Ci, Ge, Cl
6	Exchange of cup	MRSE	Cl, Ri	5	Enterobacter cloacae	Le, Ri	-
10	Exchange of cup (3x)	Staph. epidermidis	-	2	-	Le, Ri	-
15	Arthroscopy with synovectomie	Staph. epidermidis	Le, Ri	1	MRSE	Va	Ox, Ge, Cl, Ce, Im
16	-	Candida albicans	-	3	MRSE	Cl	Ox, Ge, Ce, Im
17	2x two-stage revision, 1x tibial exchange	Enterobacter cloacae	Me	7	MRSE	Va, Mo, Ri	Ox, Ge, Ce, Im

MRSE = methicillin-resistant staphylococcus epidermidis, Ox = oxacillin, Ri = rifampicin, Le = levofloxacin, Ci = ciprofloxacin, To = tobramycin, Fl = flucloxacillin, Ge = gentamicin, Cl = clindamycin, Ce = cefuroxime, Va, = vancomycin, Li = linezolid, Im = imipenem, Ti = tigecycline, Am = amoxicillin, Amp = ampicillin, Mo = moxifloxacin, Me = meropenem

Table 5: Failure rates after failed revisions due to periprosthetic infection.

Author	First Revision	Second Revision	Failure-rate
Stammers et al. [24]	Two-stage revision	Two-stage revision	42% (8/19)
Sherrell et al. [25]	I&D	Two-stage revision	34% (28/83)
Pagnano et al. [26]	Two-stage revision	Resection arthroplasty	19% (3/16)
	Two-stage revision	Two-stage revision	73% (8/11)
Current study	Two-stage revision	I&D	32% (6/19)

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request. The paper was accepted by SICOT as a poster presentation at the 37th Orthopaedic World Congress in Rome, 2016

Disclosure

Level of Evidence is therapeutic study, Level III.

Conflicts of Interest

Dr. Boettner reports personal fees from Smith & Nephew and Ortho Development Corporation, outside the submitted work. Dr. Faschingbauer reports personal fees from Deutsche Forschungsgemeinschaft (Research Fellowship, FA 1271/1-1, www.dfg.de [http://www.dfg.de]), during the conduct of the study. Neither the above-mentioned companies nor any outside organization has participated in study design or has any conflicts of interest.

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Research Article

Periprosthetic Joint Infection Does Not Preclude Good Outcomes after a Revision Total Knee Arthroplasty: A 7-Year Follow-Up Study of 144 Retrospective Cases

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Background and Purpose. Debate exists on whether septic revision total knee arthroplasty (TKA) results in inferior clinical outcomes, and limited information is available regarding the factors associated with such outcomes. This study aimed to (1) compare clinical outcomes and characteristics of aseptic versus septic revision TKA and (2) identify the risk factors associated with inferior clinical outcomes. *Methods*. We retrospectively reviewed 144 revision TKAs (90 aseptic and 54 septic revisions) that were followed for a minimum of 3 years (mean = 7 years). Clinical outcome data, namely, Knee Society knee and function scores and the Hospital for Special Surgery knee score, were collected. We reviewed 13 pre- and intraoperative variables. *Results*. Postoperative clinical outcomes were inferior in septic revision surgeries ($p<0.05$). In regression analyses, however, septic revision was not an independent risk factor for poor clinical outcomes. The independent risk factors for poor outcome were identified where Anderson Orthopedic Research Institute grade 3 femoral and tibial bone defects, more than three surgeries, and treatment for persistent infection were associated with inferior clinical outcomes (all $p<0.05$). Standard two-stage septic revision without grade 3 bone defects or additional surgeries showed comparable outcomes to aseptic revision. *Interpretation*. Clinical outcomes of septic revision were inferior to those of aseptic revision. However, poor outcomes were mainly associated with large bone defects and an increased number of surgeries. The outcomes of aseptic and septic revision surgery were similar when patients with larger bone defects and more than three surgeries were excluded.

1. Introduction

More than 650,000 total knee arthroplasties (TKAs) are performed annually in the United States [1]. As the geriatric population increases, the number of TKAs is expected to increase; subsequently, the demand for revision surgery will also increase [1]. Revision surgery is a complex, demanding procedure and, importantly, clinical outcomes are less satisfying than those of primary TKA [2, 3].

It is generally accepted that the etiology of revision surgery influences the outcome. Of the major etiologies for revision surgery, septic revision is associated with the worst outcome [2–8]. Before the introduction of two-stage revision surgeries, eradication of infection was less common; and consequently clinical outcomes were rather poor [9].

As treatment strategies for septic revision have improved, identification of organisms, eradication rates, and clinical outcomes have also improved impressively [10–14]. Some authors have reported that septic and aseptic revision groups have had similar outcomes regarding pain, functional scores, survival, and mental health status [10–12]. Patil et al. even reported a higher clinical score with septic versus aseptic revisions [11]. Recent literature has suggested that when a standard protocol and team-based approach are used, periprosthetic infection does not preclude a good outcome after revision TKA [10–12]. Hence, there is now debate regarding whether septic revision is associated with poor clinical outcomes.

Such debate regarding the clinical outcomes of septic versus aseptic surgery suggested to us that focusing on the "cause of revision" may mean that something more important is missed. Of note, revision surgeries comprise diverse clinical situations. Unlike primary TKA, revision surgeries are associated with various degrees of bone defect, different

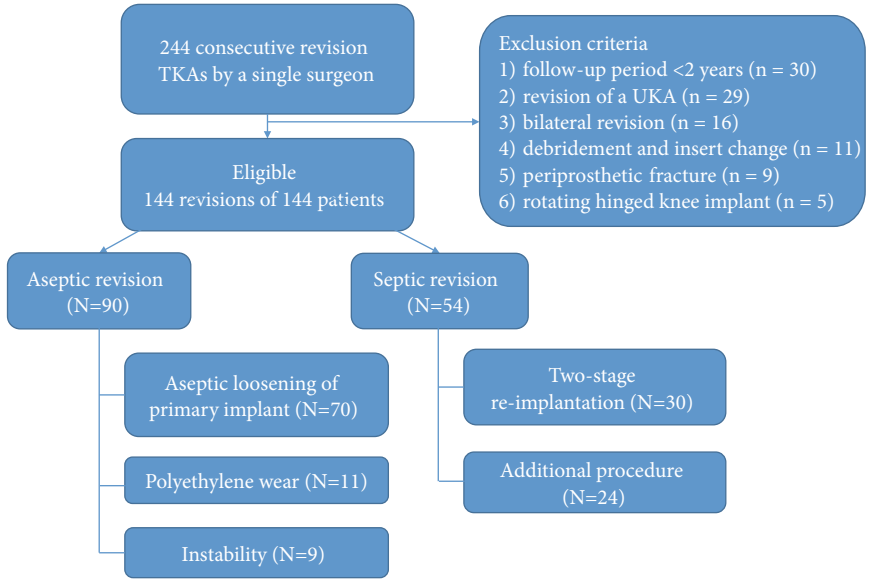

Figure 1: Flow chart of the study subjects.

implant configurations, the use of a more extensive surgical approach, and the need for repeat surgeries [7, 15, 16]. Hence, we hypothesized that the cause of the revision, especially infection, could be a confounding factor and that other unknown factors associated with infection could be more directly related to clinical outcomes. However, limited information is currently available regarding the factors associated with inferior clinical outcomes in revision TKAs with mid- to long-term follow-up. Information regarding this subject would help to improve the clinical outcome of revision TKA. Therefore, this study aimed to (1) compare clinical outcomes of aseptic versus septic revision TKA and (2) identify risk factors associated with inferior clinical outcomes.

2. Materials and Methods

2.1. Study Subjects. This retrospective study was approved by our local Institutional Review Board (Protocol No: 1307-114-506). We reviewed a single institution database of 244 consecutive revision TKAs performed by a single surgeon from 1995 to 2015. Based on the following criteria, 100 revisions were excluded: (1) follow-up period less than 2 years or loss (n = 30); (2) revision of a unicompartmental knee arthroplasty (n = 29); (3) bilateral revision (n = 16); (4) acute hematogenous infection that was successfully treated with debridement and insert change (n = 11); (5) periprosthetic fracture that required revision TKA (n = 9); and (6) rotating hinged knee implant (n = 5). This left 144 revisions of 144 patients (Figure 1). The study group included 20 males and 124 females with an average age of 68.4 years (range: 50–83 ± 7.2 years). The aseptic revision group included 70 cases with aseptic loosening of the primary implant, 11 cases with polyethylene wear, and 9 cases with instability. Both component revisions (Femur and Tibial component) were performed for all aseptic revisions. The septic revision group included 30 cases with chronic infection that were treated with two-stage reimplantation and 24 cases that underwent an additional arthrotomy and debridement for persistent infection, before or after two-stage reimplantation.

The average length of follow-up after revision was 84 ± 28.7 months (range: 40–168 months), and the average interval between the primary and revision surgeries was 99 ± 58.7 months.

During the study period, revision surgery was performed with either a varus-valgus constrained implant (LCCK®, NexGen®, Zimmer, Warsaw, IN, USA) or a posterior stabilized implant (LPS®, NexGen®, Zimmer, Warsaw, IN, USA), depending on the stability [16]. A fluted titanium extension stem, titanium block, and/or strut allograft were used, depending on the bone defect. Contained bone defects <5 mm thick were filled with bone cement. Uncontained bone defects ≤10 mm thick were treated with block augment and uncontained bone defects >10 mm thick were treated with strut allografts using screw fixation (Figure 2). Stem extensions were fixed using the hybrid fixation technique for the entire implant. Intraoperative observations were systemically collected using a predesigned database. Bone defects were classified according to the Anderson Orthopedic Research Institute (AORI) bone defect protocol [17]. Two independent investigators prospectively collected all the clinical information using the predesigned computer database (SMA and EMS). Basic demographic data and clinical outcomes, including the Knee Society Knee score (KSKS) and Knee Society function score (KSFS), and the Hospital for Special Surgery knee score (HSS) were recorded. Postrevision outcomes were collected annually and the most recent follow-up data were used. ROM was measured from maximum extension to maximum flexion using a standard clinical goniometer with the patient in the supine position.

2.2. Protocol of Septic Revision Surgery. For patients with a chronic periprosthetic infection, a two-stage reimplantation

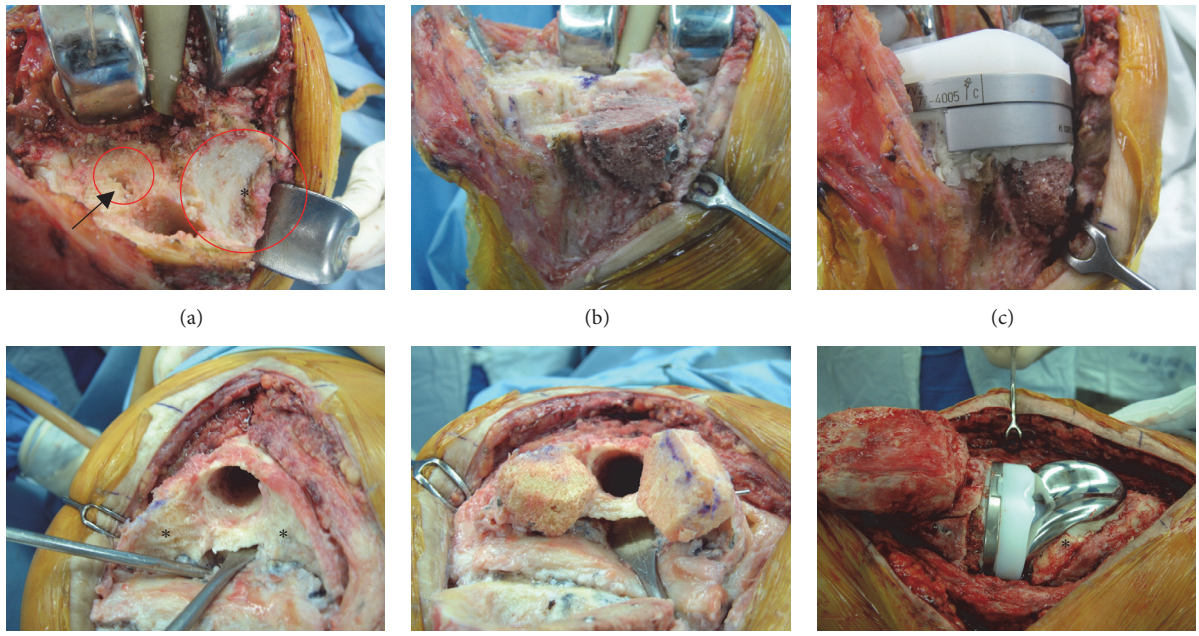

FIGURE 2: Bone defect filling process. (a) Intraoperative photograph showing an unconstrained, large bone defect with destruction of the metaphyseal bone (grade 3 bone defect) on the medial side of the tibia (asterisk) and a small, constrained bone defect (arrow) on the lateral side of the tibia. (b) Initially the large bone defect was treated with allografts using screw fixation in the metaphysis. (c) Then the remaining unconstrained bone defect was filled with a metal block and the defect on the lateral side was filled with cement. (d) Intraoperative photograph showing unconstrained large bone defect (asterisks) with destruction of major metaphyseal bone in femur (grade 3 bone defect). (e) Allograft was also used to fill the large bone defect. (f) Implant was inserted to the augmented area and the allograft was tightly compacted between femur component and remaining bone (asterisk).

was performed, which included removal of components, extensive debridement, and placement of an antibiotic-impregnated articulating cement spacer, followed by 6 to 8 weeks of intravenous antibiotics according to the microorganism. After a 4-week antibiotic free interval, we performed laboratory tests and joint aspirations to determine whether the infection has been eradicated. If so, reimplantation was performed. Debridement and replacement of the antibiotic-impregnated cement spacer were performed instead of reimplantation if there were signs and symptoms of persistent infection. The criteria for a persistent infection included ongoing discharge and erythema, higher than 36.5°C of the body temperature, higher than 0.5 mg/dl of the C-reactive protein level, or more than five polymorphonuclear neutrophils observed on any high-power field (HPF) in 10 frozen section specimens harvested intraoperatively from the synovium or necrotic tissue debris.

2.3. Statistical Analysis. Clinical outcomes and characteristics of the septic revisions were compared with those of the aseptic revisions using Student's t-test for continuous, normally distributed data and Pearson's chi-square test for nominal, categorical data. Within both groups, the prerevision and postrevision data were compared using the paired t-test for the normally distributed data. Normality of data was assessed using the Kolmogorov-Smirnov test. For all analyses, the level of significance was set at a p value of <0.05.

To identify the factors associated with inferior clinical outcomes in revision TKAs, linear regression analyses were used. Thirteen variables were assessed, including age, sex, body mass index (BMI), the primary diagnosis (0, osteoarthritis; 1, rheumatoid arthritis), the cause (0, aseptic loosening; 1, septic loosening), prerevision ROM, implant type (0, PS implant; 1, LCCK), the surgical approach (0, standard parapatellar approach; 1, quad-snip; 2, V-Y quadriceps plasty; and 3, tibial tubercle osteotomy), the femur bone defect (AORI type 1, 2, or 3), the tibia bone defect (AORI type 1, 2, or 3), complications (0, no complication; 1, a complication present), insert thickness, and number of operations (arthrotomy operation). Factors with a p value < 0.20 on univariate analysis were assessed subsequently through multivariate analysis using the stepwise method. Statistical analyses were performed using the SPSS® for Windows® statistical software package (ver. 19.0.1; SPSS Inc., Chicago, IL, USA).

3. Results

The preoperative clinical outcomes were similar between the aseptic versus septic revision groups (Figure 3). However, the preoperative ROM was higher in the aseptic revision group ($p<0.001$). In both groups, all clinical outcomes (KSKS, KSFS, and HSS scores) improved after revision ($p<0.001$) as did the ROM. However, the final scores were less satisfying in the

Table 1: Characteristics of the study groups.

	Aseptic revision (n = 90) Mean ± SD	Septic revision (n = 54) Mean ± SD	P-value
Age (years)	69.1 (50–83)	67.2 (50–80)	0.095
Female gender	85 (94.4%)	39 (72.2%)	<0.001
Body mass index (kg/m^2)	28.0 ± 4.4	25.9 ± 3.6	0.007
Average polyethylene thickness (mm)	16.6 ± 3.29	16.2 ± 3.3	0.621
Varus-valgus constrained implant	61 (67.8%)	50 (92.6%)	<0.001
Surgical approach			
Standard parapatellar approach	64 (71.1%)	26 (48.1%)	0.008
Extensive approach	26 (28.9%)	28 (51.9%)	
Bone defect			
Grade 1 / 2 / 3 femoral bone defect	30 / 55 / 5	4 / 37 / 13	<0.001
Grade 1 / 2 / 3 tibial bone defect	32 / 53 / 5	20 / 27 / 7	0.256
Average number of surgeries	1.01	2.7∗	<0.001
Wound complications	1 case	6 cases	0.011
Average time interval between primary and revision surgery (months)	127 ± 35	53 ± 28	<0.001

Values are means ± standard deviations or percentages.
∗Two-stage revision, 30 cases; three- or four-stage revision, 24 cases.

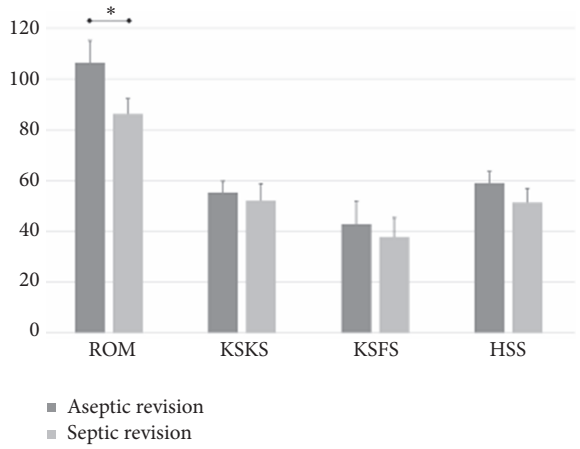

Figure 3: Characteristics and clinical scores of each revision group. Preoperative ROM was significantly greater in the aseptic revision group. Values are means and standard deviations, and the asterisk denotes statistical significance. ROM, range of motion; KSKS, Knee Society knee score; HSS, Hospital for Special Surgery knee score.

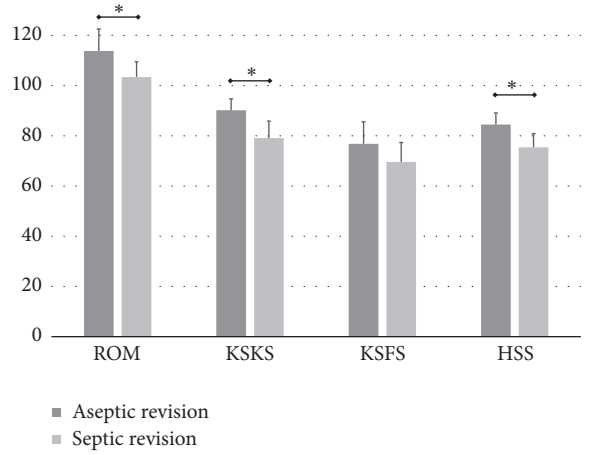

Figure 4: Postoperative outcomes of each revision group. Postoperative ROM, KSKS, and HSS were significantly lower in the septic revision group. Values are means and standard deviations, and asterisks denote statistical significance. ROM, range of motion; KSKS, Knee Society knee score; HSS, Hospital for Special Surgery knee score.

septic revision group. The postrevision ROM, KSKS score, and HSS score were significantly lower (p=0.030, <0.001, and 0.003, respectively). Only the KSFS score was similar between the two groups (p=0.105, Figure 4).

Regarding the pre- and intraoperative factors, constrained implant was more frequently used in the septic revision group (p<0.001) and a more extensive approach was chosen (p=0.008) (Table 1). Repeated surgery was required in the septic revision group ($p<0.001$) and complications were more frequent (p=0.011). Also, the femoral bone defects tended to be more extensive (p<0.001).

Univariate and subsequent multivariate linear regression analyses were performed to identify factors that were associated with clinical outcomes and ROM (Tables 2 and 3). Regression analysis revealed that the postrevision ROM increased with age (p=0.001) and greater prerevision ROM (p<0.001) and decreased with tibia bone defects (both grades 2 and 3, p<0.001 and p<0.002, respectively) and three or four surgeries (p<0.001). We performed the same analysis for the remaining clinical outcomes and showed that femoral bone defects (grade 3), tibial bone defects (grade 3), and the three or four surgeries were strongly associated with inferior

Table 2: Results of univariate regression analysis including 13 pre- and intraoperative variables and four clinical outcomes.

	ROM		KSKS		KSFS		HSS	
Variable	$\beta \pm$ SE∗	P-value	$\beta \pm$ SE∗	P-value	$\beta \pm$ SE∗	P-value	$\beta \pm$ SE∗	P-value
(1) Age	0.8±0.2	<0.001	0.1±0.2	0.339	0±0.2	0.891	0.2±0.2	0.233
(2) Female gender	1.5±4.6	0.742	3.9±3.2	0.227	0.6±4.3	0.885	0.7±3.3	0.842
(3) Body mass index	0.5±0.4	0.259	0±0.3	0.996	0±0.4	0.919	−0.1±0.3	0.837
(4) Primary diagnosis								
Osteoarthritis (comparator)								
Rheumatoid arthritis	−7.2±6.6	0.279	−1.9±4.8	0.697	−7.5±6.5	0.249	−7.4±4.9	0.132
Other	−3.6±8	0.659	3±5.5	0.590	2.2±7.5	0.771	4.5±5.6	0.425
(5) Cause	−5.3±1.6	0.001	−4.8±1.1	<0.001	−3.7±1.5	0.017	−4.7±1.1	<0.001
(6) Preoperative ROM	0.3±0.1	<0.001	0.1±0	0.014	0.1±0.1	0.028	0.1±0	0.016
(7) Implant	−2.8±3.8	0.460	−3.8±2.6	0.145	−8.4±3.5	0.016	−5.6±2.6	0.034
(8) Standard paramedian approach (comparator)								
Quadriceps snip	−7±3.6	0.056	−6.9±2.5	0.006	−10.5±3.3	0.002	−5.2±2.6	0.046
VY quadriceps plasty	−1±5.8	0.866	7.3±3.9	0.066	11.2±5.3	0.037	8±4	0.049
Tibial tubercle osteotomy	−8.4±6.6	0.207	−5.7±4.5	0.208	1.2±6.2	0.85	−7.7±4.9	0.118
(9) Grade 1 femur bone defect (comparator)								
Grade 2	−5.1±3.3	0.125	0.9±2.3	0.696	−2.6±3.1	0.397	0.1±2.3	0.955
Grade 3	−21.5±4.8	<0.001	−21.6±3.1	<0.001	−18.5±4.5	<0.001	−18.7±3.2	<0.001
(10) Grade 1 tibial bone defect (comparator)								
Grade 2	−10±3.1	0.002	−4.3±2.2	0.051	−8.6±2.9	0.018	−5.2±2.2	0.022
Grade 3	−20.8±6.4	0.001	−13.7±4.4	0.002	−13.7±6.1	0.026	−11.8±4.8	0.016
(11) Insert thickness	0.4±0.6	0.499	0.1±0.4	0.780	0.3±0.5	0.562	0±0.4	0.978
(12) Wound complications	−16.6±7.9	0.038	−8.7±5.5	0.115	−4.4±7.5	0.555	−18.8±5.4	0.001
(13) Single surgery (comparator)								
Two-stage	5.2±3.9	0.19	−2.1±2.7	0.448	−5.2±3.7	0.164	1.5±2.8	0.584
Three- or four-stage	−22.3±3.8	<0.001	−15.5±2.7	<0.001	−7.9±3.9	0.025	−16.9±2.6	<0.001

∗Values are standardized regression coefficients (β) ± standard errors (SE). ROM, range of motion; KSKS, Knee Society knee score; HSS, Hospital for Special Surgery knee score; KSFS, Knee Society function score

Table 3: Results of multivariate regression analysis: relationships between selected variables and four clinical outcomes∗.

Multivariate analysis	ROM		KSKS		KSFS		HSS	
Variable	$\beta \pm$ SE†	P-value	$\beta \pm$ SE†	P-value	$\beta \pm$ SE†	P-value	$\beta \pm$ SE†	P-value
Age	0.6±0.2	0.001						
Cause of revision								
Preoperative ROM	0.2±0.1	<0.001						
Grade 1 femur bone defect (comparator)								
Grade 2			−5.8±2.0	0.005	−10.2±3.2	0.002		
Grade 3			−21.6±3.4	<0.001	−25.6±4.9	<0.001	−12.9±3.1	<0.001
Grade 1 tibial bone defect (comparator)								
Grade 2	−12.9±2.5	<0.001						
Grade 3	−16.7±5.3	0.002					−5.5±1.9	0.004
Single surgery (comparator)								
Two-stage								
Three- or four-stage	−16.1±3.3	<0.001	−10.2±2.5	<0.001			−13. 3±2.5	<0.001
R^2_{adj} ‡	0.45		0.36		0.16		0.34	

∗Variables with p<0.20 in the univariate analysis were included in the multivariate analysis (stepwise method). Nonsignificant factors were excluded from the table. ROM, range of motion; KSKS, Knee Society knee score; HSS, Hospital for Special Surgery knee score.

†Values are $\beta \pm$ SE.

‡R^2_{adj}, percent variance explained by each variable.

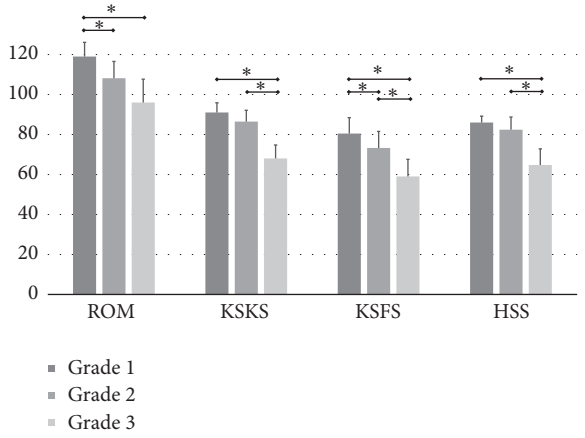

Figure 5: Clinical outcomes according to the severity of the femoral bone defect. Grade 3 bone defects showed inferior outcomes compared to grade 1 and 2 defects. Values are means and standard deviations, and asterisks denote statistical significance. ROM, range of motion; KSKS, Knee Society knee score; HSS, Hospital for Special Surgery knee score.

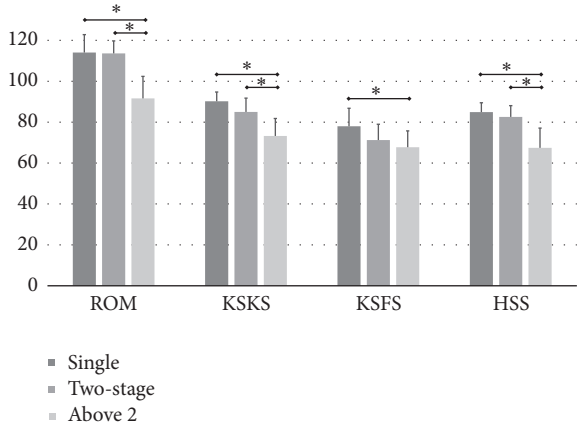

Figure 6: Clinical outcomes according to the number of surgeries. Outcomes were inferior with more than two surgeries compared with single- or two-stage surgery. Values are means and standard deviations, and asterisks indicate statistical significance. ROM, range of motion; KSKS, Knee Society knee score; HSS, Hospital for Special Surgery knee score.

clinical outcomes in revision TKA. Specifically, the KSKS, KSFS, and HSS scores were related to grade 3 femoral bone defects, ROM and HSS to grade 3 tibial bone defects, and ROM, KSKS, and HSS scores to having three or four surgeries. However, the cause of revision was not associated with the clinical outcomes.

Postrevision clinical outcomes were compared according to bone defect and number of surgeries. As the degree of defective femoral bone increased, the ROM and outcome scores gradually decreased (Figure 5). The clinical outcomes of patients with a grade 3 bone defect were especially poor for every outcome score ($p<0.05$). Regarding the number of surgeries, three or four surgeries had significantly inferior outcomes ($p<0.05$). However, patients that had only a two-stage revision in the absence of large bone defects did similar to aseptic revisions (Figure 6).

4. Discussion

The most important finding of our study was that inferior clinical outcomes in revision TKA surgery were related to large bone defects (grade 3) and greater numbers of surgeries (more than three) and not with the type of revision (septic vs. aseptic revision). Septic revision was not directly related to clinical outcomes per se; instead it was indirectly related with an increased number of surgeries and larger bone defects, which are characteristics of persistent infection after failure to control the initial infection. Our data showed that the outcomes of aseptic and septic revision surgery were similar if patients with larger bone defects and more than three surgeries were excluded.

There is debate regarding whether septic revision results in inferior clinical outcomes [2–8, 10–12]. Barrack et al. reported that septic revision was associated with significantly lower functional scores [4]. However, patients undergoing second or third revisions were included. Van Kempen et al. reported a similar result, but they did not report on the bone defects encountered or the number of revisions [8]. Patil et al. reported higher clinical scores after septic revisions than after aseptic revisions [11]. However, they included polyethylene exchange and chronic osteomyelitis patients in their analyses. We believe that these inconsistent results originate from the complexity of revision surgery. Most previous reports simply compared septic versus aseptic revision surgery. However, septic revision encompassed various clinical situations, including large bone defects and even failed infection control. It is not "inappropriate" to state that septic revisions have poorer outcomes. That is a fact. However, it is not the infection that is an independent risk factor but rather the size of the bone defect and the number of surgeries.

Limited information is available regarding the factors affecting clinical outcomes in revision surgery. It has been reported that aggressive microorganisms, chronic lymphedema, repeated surgery, and comorbidities increase the failure risk of revision surgery and also result in poor clinical outcomes [18–20]. Although previous studies have focused mainly on the success rate of revision surgery, we believe their findings are in line with our research.

Extra surgical procedures over a two-stage surgery (3rd or 4th surgery) resulted in inferior clinical outcomes. These patients had a decreased ROM as well as poorer functional and pain scores. Repeated tissue injury that results in persistent inflammation with tissue degeneration and emotional depression due to prolonged hospitalization may lead to inferior clinical outcomes for these patients [21–23]. In fact, we often see patients who are depressed and disappointed that the infection was not controlled even after debridement or a two-stage surgery. It is notable that extra surgical procedures (more than two-stage) most commonly occurred due to failed infection control. Sherrell et al. reported that failure of irrigation and debridement leads to subsequent failure of two-stage reimplantation and ultimately requires

another operation for persistent infection [24]. Our findings suggest that failure to control infection in a two-stage surgery or an inappropriate treatment decision for periprosthetic infection may result in poor clinical outcomes. We would expect satisfactory clinical outcomes for septic revision with a standard treatment protocol.

Several studies have reported poor outcomes for revision TKA of larger bone defects. Franke et al. reported that 20% of patients experienced a poor outcome in their 5-year follow-up, and Clatworthy et al. reported a 72% 10-year success rate, meaning that one of four patients required re-revision surgery [25, 26]. In our case, there were 7 failures among 18 grade 3 femoral bone defects. The most common reason was loosening of the implant, of which there were three cases that eventually required re-revision. The second most common reason was infection. Two patients required arthrodesis. The third most common reason was instability, as two patients required a knee brace but they declined a further procedure. Reconstruction techniques other than an allograft should be considered to solve these problems. Although it is currently unclear why femoral bone defects were more related to a poor outcome than were tibial bone defects, efforts should be made to reduce bone defects, especially of the femur, during revision TKA. In our experience, a motorized burr is better than a curette and osteotome for preserving healthy bone during debridement.

Readers should be aware of several limitations of the current study. First, due to the retrospective nature of the study and the scarcity of revision cases, we could not effectively control the baseline demographics. Thus, gender and BMI in this study differed between the aseptic and septic groups, introducing the possibility of selection bias. Although a matched study would be more desirable, it is actually impossible to match perfectly or stratify subjects while maintaining statistical power in a revision study. Thus, we used multiple regression analysis to correct for confounding bias of independent variables affecting the clinical outcomes. Despite the limitations, the statistical power of our regression model was sufficient to validate our outcome. Second, a considerable amount of variance in our multivariate model remained unexplained. This indicates that other unknown factors, such as combined spine pathology, general health status, quadriceps muscle strength, presence of microorganisms, and mental health, may have been related to the clinical outcomes [22, 23, 27, 28]. However, the value of such information is limited as these variables cannot be modified during the surgical procedure. We believe that our evaluation of 13 variables included most of the intraoperative and surgically correctable factors and provided information that was relevant to improving the clinical outcome. Third, the female predominance of the study population should be noted. The proportion of females was 83.8%, which was substantially higher than that reported by other studies of outcomes of revision surgery [2–8, 10–12, 29, 30]. Although there is no clear explanation for the female predominance in knee osteoarthritis, it has been consistently reported in several epidemiologic studies [31, 32]. This predominance is even greater in Koreans; consequently, the incidence of TKA is 7-8-fold higher in females than in males [33]. This could explain the predominance of females in this study and indicates that the possible selection bias was negligible.

5. Conclusions

Clinical outcomes of septic revision were inferior compared to those of aseptic revision. However, poor outcomes mainly resulted from large bone defects and a high number of surgeries. The outcomes of aseptic and septic revision surgery were similar when patients with larger bone defects and more than three surgeries were excluded from the analyses.

Conflicts of Interest

All authors declare that they do not have any conflicts of interest.

Authors' Contributions

Du Hyun Ro contributed to planning, statistical analysis, and writing of the manuscript; Jong-Keun Kim contributed to data analysis and revision of the manuscript; Sunghwan Kim contributed to planning and editing of the manuscript; Hyuk-Soo Han contributed to revision of the manuscript and data analysis; Myung Chul Lee contributed to planning, statistical analysis, and writing and editing of the manuscript.

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Review Article

Do Culture-Negative Periprosthetic Joint Infections Have a Worse Outcome Than Culture-Positive Periprosthetic Joint Infections? A Systematic Review and Meta-Analysis

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Background. Culture-negative periprosthetic joint infections (CN PJI) have not been well studied, and due to the lack of consensus on PJI, especially with culture-negative infections, there are considerable uncertainties. Due to the challenging clinical issue of CN PJI the aim of this systematic review is to describe incidence, diagnosis, and treatment outcomes based on the current literature on CN PJI. *Hypothesis.* The review is designed to assess the formal hypothesis that CN PJI of the hip and knee have a poorer outcome when compared with culture-positive ones. *Study Design.* It is systematic review with level of evidence 3. *Methods.* EMBASE, MEDLINE, and the Cochrane Library were searched electronically in January 2018. All studies regarding CN PJI of the hip or knee published in English or German with a minimum of 10 patients were included. Afterwards, the authors performed a descriptive analysis of diagnosis and treatment outcome. *Result.* Eight studies were identified that met the inclusion criteria. The incidence of CN PJI in the hip or knee ranged from 7% to 42 %. The included studies were pooled to give an overall incidence rate estimate of 11 % [95% confidence interval (CI): 10-12] based on a random-effects model. The most common surgical intervention was the two-stage revision of prosthesis with 283 patients. Postoperatively, the majority of patients received vancomycin as the antibiotic treatment, alone or in combination with other antibiotics. The rate of succesfully treated infections varied from 85% to 95 % in all included studies. The two-stage exchange arthroplasty had the best outcome, based on the infection-free survival rate of 95%, five years after treatment. *Conclusions.* We conclude that CN PJI have the same or even better results than culture-positive infections. Nonetheless, a standardized diagnostic protocol and evidence-based treatment strategies for CN PJI should be implemented for further studies.

1. Introduction

When performing arthroplasty of the hip or knee, periprosthetic joint infections are among the most serious complications after the procedure. 1% of all hip replacements and 2-3% of primary knee prostheses are affected [1, 2]. In the future, a rise in infections is likely due to an increase of implantations, increasing lifespans of patients and the resultant longer prostheses retention times.

Due to a lack of consensus on diagnosis and treatment of periprosthetic joint infections, especially culture-negative infections, there still seem to be considerable uncertainites. Different diagnostic protocols for detecting periprosthetic joint infections have been published, and hence there seems to be no standardized protocol being used across studies [3–13].

Moreover, comparisons of treatment outcomes are difficult to make, as the current evidence does not conclusively support a superior treatment strategy for periprosthetic joint infections.

The culture-negative periprosthetic joint infection is even more demanding in diagnosis and treatment, as without positive culture the uncertainty about the correct diagnosis of infection grows. Without knowing the causing microorganism, it is a challenge to determine the right treatment and choice of antibiotics for any patient. This is all the more difficult due to the sparse existing literature on the treatment and outcome of CN PJI.

Table 1: Search strategy.

Search #	Query
#1	periprosthetic infection or periprosthetic joint infection or surgical wound infection or prosthesis-related infection
#2	knee arthroplasty or total knee arthroplasty or knee replacement or knee prosthesis or arthroplasty, replacement, knee
#3	hip arthroplasty or total hip arthroplasty or hip replacement or hip prosthesis or arthroplasty, replacement, hip
#4	Culture negative OR culture
#6	#1 AND #2 AND #4
#7	#1 AND #3 AND #4

This systematic review therefore aims to give an overview on the current database of studies concerning culture-negative periprosthetic joint infections of the hip and knee. The different diagnosis protocols and results after treatment were analyzed, and whether culture-negative infections really have a worse outcome when compared to culture-positive ones was evaluated.

2. Material and Methods

In January 2018 the authors conducted a systematic literature search of MEDLINE, EMBASE via OvidSP, and the Cochrane Library addressing culture-negative periprosthetic joint infections. To identify additional studies that possibly fit the criteria and had not been discovered via the electronic database search, the authors reviewed the bibliographies of the chosen studies and review articles. The systematic review has been reported in accordance with the PRISMA statement [14]. See Table 1 for search terms used.

Inclusion criteria comprised studies published in English or German, numbers of patients >10, and studies regarding culture-negative periprosthetic joint infections after arthroplasty of the knee or hip. Although two-stage exchange arthroplasty is the most widely performed procedure, all treatment strategies were included in the search. Studies with prosthetic joint infections of another region than knee or hip were excluded, as well as case reports, review articles, opinion of experts, and letters to the editors. The abstracts of the selected studies were screened. If they were found to be inadequate, the full text was evaluated to determine whether a study was eligible for inclusion. Two of the authors independently carried out the process described above. Lack of consensus was resolved by thorough discussion. A level of evidence based on The Journal of Bone and Joint Surgery guidelines was then assigned to every article. Different variables for a comparative analysis of the outcome of each study were included in a data sheet (Table 2). A descriptive review of the variables, such as the infection control rate and outcome of the included studies, was drafted, and a comparison between all studies was performed. The included studies were pooled to give an overall incidence rate based on a random-effects model with 95% confidence interval (CI). Heterogeneity between the studies was assessed with a chi-square-test and quantified with I^2 statistics. Publication bias was evaluated with funnel plot analysis.

3. Results

A flow chart of our literature research was created using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1).

532 potential studies matching our inclusion criteria were identified via the search strategy and manual screening of the bibliographies of relevant studies. We excluded 477 studies after reviewing title and abstract. This left 49 full-text studies to be assessed for eligibility. Finally, 8 papers were selected for inclusion in our systematic review and meta-analysis [15–22].

Table 2 shows short summaries of the results of all included studies. All studies have retrospective character and lower quality, with level III of evidence based on The Journal of Bone and Joint Surgery guidelines. All studies were published between 2007 and 2017. The incidence rate of culture-negative periprosthetic infections in the hip or knee ranged from 7% to 42 % with a total number of all included patients being 3,342. Of these, 504 were culture-negative (Figure 2). The included studies were pooled to give an overall incidence rate estimate of 11 % [95% confidence interval (CI): 10-12] based on a random-effects model (Figure 3).

Funnel plot analysis of included studies assessing the overall incidence of CN PJI revealed a publication bias (Figure 4). 36% of all included culture-negative cases were periprosthetic hip infections, and 64% were prosthetic knee infections. A total number of 137 patients were treated for irrigation and debridement with retention of the prosthesis, 16 patients with one-stage exchange arthroplasty, 42 with permanent resection of the joint, and 26 patients with other treatment options like chronic antibiotic suppression. The two-stage revision of prosthesis was the most common surgical intervention with a total number of 283 patients. The studies differ in the diagnostic protocols used to identify culture-negative infections. Often the diagnostic criteria of the Musculoskeletal Infection Society [8] are used as a reference. To better compare the included studies, a graphic was created (Figure 5).

As a postoperative antibiotic, vancomycin was used to treat most of the patients in the included studies, either alone or in combination with other antibiotics. In the studies of Berbari et al. and Malekzadeh et al. cephalosporins were more commonly used to eliminate a periprosthetic joint infection. The relevant studies documented prior use of antibiotics as a risk factor for culture-negative periprosthetic infections.

The included studies define a successful treatment with variable parameters [15–22]. Intersections of the parameters

Table 2: Data sheet for comparative analysis [15–22].

Author	Li H et al.	Choi HR et al.	Ibrahim MS et al.	Huang R et al.	Berbari EF et al.	Malekzadeh D et al.	Kim YH et al.	Kim YH et al.
Title	Two-stage revisions for culture-negative infected total knee arthroplasties: A five-year outcome in comparison with one-stage and two-stage revisions for culture-positive cases.	Periprosthetic joint infection with negative culture results: Clinical characteristics and treatment outcome.	Two-stage revision for the culture-negative infected total hip arthroplasty.	Culture-negative periprosthetic joint infection does not preclude infection control.	Culture-negative Prosthetic Joint Infection.	Prior Use of Antimicrobial Therapy is a Risk Factor for Culture-negative Prosthetic Joint Infection.	Comparison of infection control rates and clinical outcomes in culture-positive and culture-negative infected total-knee arthroplasty.	The outcome of infected total knee arthroplasty: culture-positive versus culture-negative.
Year	2017	2013	2017	2012	2007	2010	2015	2015
Country	Netherlands	United States	UK	United States	United States	United States	Korea	Korea
LoE	III	III	III	III	III	III	III	III
Study design	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
Study Type	Case-Control study	Case-Control study	Case-Control study	Case-Control study	Cohort study	Case-Control study	Case-Control study	Case-Control study
Treatment interval	2003-2014	2000-2009	2007-2012	2000-2007	1990-1999	1985-2000	2001-2008	1991-2008
Total number of cases	129	175	-	295	897	1413	242	191
Prevalence of CN cases %	14.2	23	-	16.3	7	10.5	42.1	26.7
Hip %	-	50	100	43.8	45	50	-	-
Knee %	100	50	-	56.2	55	50	100	100
FU in months, median	55.6	52	60	47	36-60	56	127.2	127.2
Risk factors		-	(1) prior use of antibiotics (2) referral from elsewhere (3) age		(1) prior use of antibiotics (within 3 months)	(1) prior use of antibiotics (in 64%) (2) prolonged wound drainage after index arthroplasty (residual confounder)	-	-
Debridement n	-	11	-	12	12	18	56	28
1-stage n				3	5	8	-	-
2-stage n	18	23	50	33	34	56	46	23
Permanent resection n		-	-	-	8	34	-	-
Other therapy		6	-	-	1	19	-	-
Antibiotic treatment after diagnosis %	Vancomycin 33 Vancomycin + Ceftriaxone 33 Others 34	Vancomycin 70; Others 30	-	Vancomycin 81; Cephalosporins 10; Others 9	Cephalosporins 82; Vancomycin 12; Others 6	Cefazolin 69; Vancomycin 13; Others/None 18	Vancomycin 85; Others 15	Vancomycin 86; Others 14
Successful treatment in %	88,9	85	94	-	-	-	95	95

Table 2: Continued.

Author	Li H et al.	Choi HR et al.	Ibrahim MS et al.	Huang R et al.	Berbari EF et al.	Malekzadeh D et al.	Kim YH et al.	Kim YH et al.
Overall infection free survival rate % 1.) 3-year 2.) 5-year	-	-	1.) - 2.) 94	73	-	1.) - 2.) 67	-	-
I&D infection free survival rate % 1.) 3-year 2.) 5-year	-	-	-	50	1.) - 2.) 71	78	57	61
2-Stage infection free survival rate % 1.) 3-year 2.) 5-year	1.) 75 2.) 95	-	-	58	1.) - 2.) 94	1.) 87 2.) 79	83	83
1-Stage infection free survival rate % 1.) 3-year 2.) 5-year	-	-	-	100	-	-	-	-
Resection arthroplasty infection free survival rate % 1.) 3-year 2.) 5-year	-	-	-	-	1.) 51	1.) 49 2.) 43	-	-
Outcome	With combined or broad-spectrum antibiotics, two-stage revision showed comparable outcome in satisfaction rates, reinfections rates and cumulative survival rates at 5-year Follow-up with CP PJI patients.	The success rate of infection control was higher in the CN group, which suggests that CN may not necessarily be a negative prognostic factor for PJI.	-	The overall infection control rate was similar between CP and CN PJI cases (both 73%).	The outcome of CN PJI is similar to the outcome of PJI due to known pathogens.	The demographics and outcome of CP and CN PJI patients were similar (free of treatment failure at 2 years 79% and 75%).	The infection control rates and clinical outcomes were not different between CP and CN groups (overall infection control rates 90% and 95%).	Overall rates of infection control, successful treatment, and functional outcomes were not different between the CP and CN groups (overall infection control rates 90% and 95%).

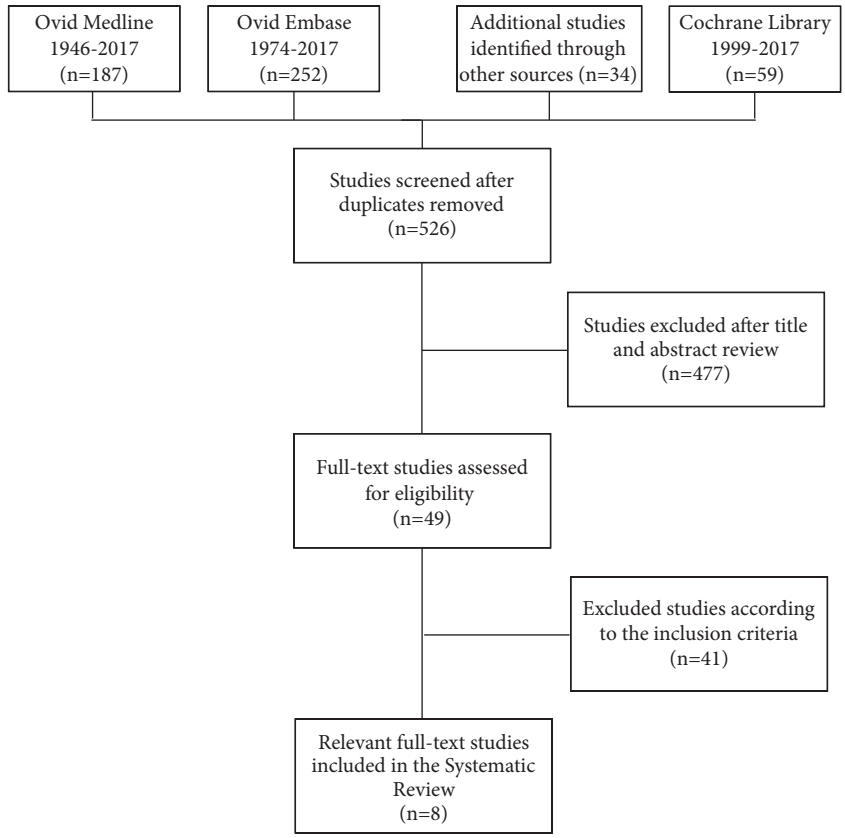

Figure 1: Flow chart.

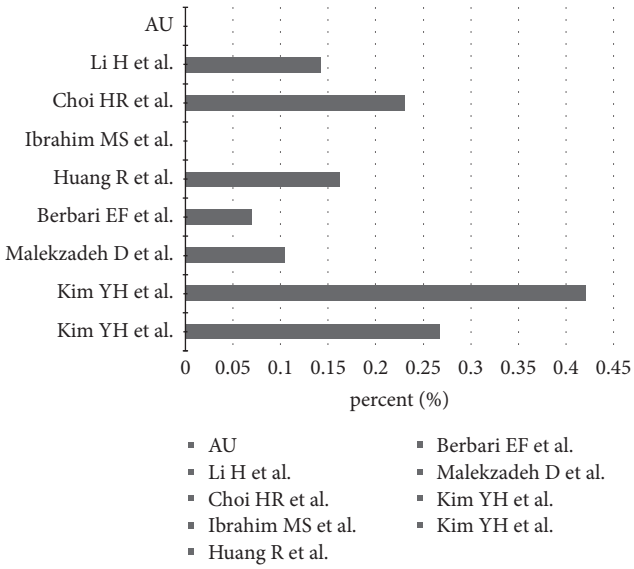

Figure 2: Range of incidence of CN PJI.

are illustrated in the following graphic, excluding Li et al. as the study did not specify parameters (Figure 6).

The rate of successful treated infections varied from 85% to 95 % in all included studies. The majority of studies observe infection-free survival rates in 3-year and 5-year time-intervals. The overall infection-free survival rate ranged from 67% to 94%. The two-stage exchange arthroplasty has the best outcome with regard to the infection-free survival rate with rates up to 95% five years after treatment. When comparing the outcomes of culture-negative periprosthetic infections with those of culture-positive periprosthetic infections, all studies came to the conclusion that culture-negative infections have the same or, in the study of Choi et al., even better results than culture-positives.

4. Discussion

Periprosthetic joint infections are serious complications that may occur after joint replacement. The incidence ranges from 2% to 3% in primary knee [1, 2] and 1% to 4% in primary hip replacement [2, 24]. In this systematic review, the incidence rate of CN PJI ranged from 7% to 42% [15–22] with a pooled incidence rate of 11%.

The aim of this study is to identify the relevant studies on culture-negative periprosthetic joint infections from the hip and knee and to analyze the reported incidences, diagnostic protocols, and treatment outcomes.

Treating a periprosthetic infection even when the causing organism is known is challenging in itself and a topic of the current investigations [25–29]. When there is no identification of the causing pathogen it is certainly an even bigger challenge. A culture-negative infection is still

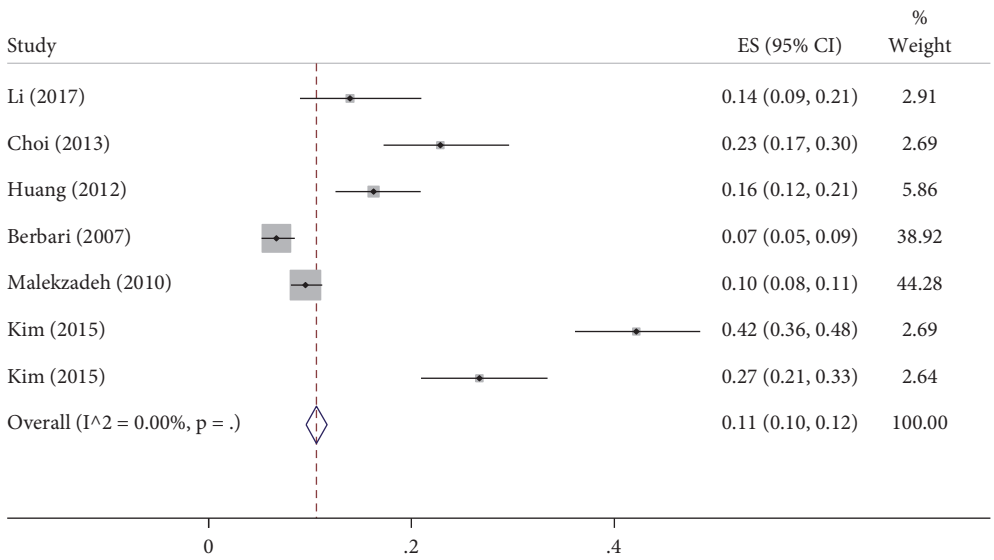

Figure 3: Rates of incidence for culture-negative periprosthetic joint infections of the hip and the knee. Summary estimates for the incidence of CN PJI were calculated using random-effects models with 95% confidence interval (CI). An I^2 value (statistical heterogeneity) of 0.00% indicates a low variability in intrastudy differences in the overall effect size.

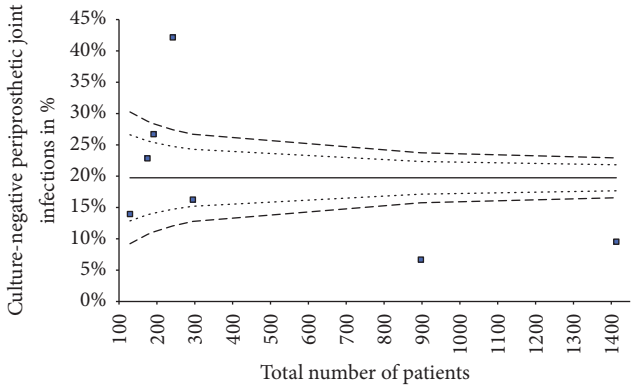

Figure 4: Funnel plot analyses.

a subject of controversy because of a lack of literature for a consistent diagnostic protocol and optimal treatment recommendations. Because there are no consistent diagnostic parameters, a comparison between the studies is complicated. While reviewing the literature, the authors found different classifications for the diagnosis of a periprosthetic joint infection (Table 3).

A consistent usage from one classification, separated from the author, joint, or location of the study was not recognizable. Renz and Trampuz et al. published a diagnostic protocol following the international recommendations for usage in further studies to make comparisons between studies and results more reliable (Table 4). In the case that the pathogen cannot be identified, there are three additional parameters to confirm the periprosthetic joint infection.

Reasons for culture-negative periprosthetic joint infections are not definitely resolved. They could include inappropriate diagnostic tools for rare organisms such as mycobacterium, fungi, and others like Brucella or Coxiella burnetti that are difficult to identify using routine methods [15, 16, 30]. The most common risk factor in our systematic review for culture-negative infection was the prior use of antibiotics [15, 18, 22] which can compromise the sensitivity of routinely used diagnostic laboratory tests. For this reason, Della Valle et al. in the clinical practice guideline of American Academy of Orthopedic Surgeons recommends that the antimicrobial treatment be interrupted at least two weeks before aspiration [5]. To increase the detection rate of the low-virulence microorganisms multiple samples (minimum 3) should be taken, and an adequate growth time of at least 14 days [2, 31] should be allowed. Emphasis is placed on new diagnostic tools for improving the sensitivity and specifying for diagnosis of culture-negative prosthetic joint infections, while reducing the number of false-negative results. Trampuz et al. demonstrated the importance of sonication of prostheses in improving diagnosis of periprosthetic joint infections of the knee and the hip, since this method attains more sensitivity than conventional periprosthetic-tissue culture, particularly in patients with prior antibiotic treatment [31]. The most common molecular biological technique is the polymerase chain reaction to detect the causing microorganism [32, 33]. Even unusual species like fungal periprosthetic joint infections could be detected with a selective medium and an increased incubation time [34]. The analyses of the synovial fluid with new biomarkers are currently validated in clinical studies [2]. The alpha-defensin test shows especially good results in detecting a periprosthetic joint infection [2, 35, 36], but it is yet to be validated in larger studies. Next-generation sequencing has recently gained attention and is a topic of current investigations to evaluate the accuracy in identifying causing microorganisms in periprosthetic joint infections, especially in culture-negative infections [37].

The outcome of PJI is determined by the choice of surgical treatment. There are different treatment strategies, including

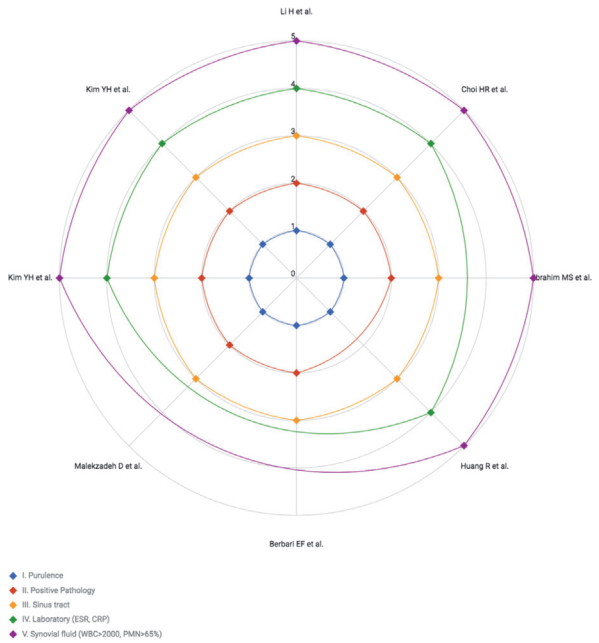

Figure 5: Definition of diagnosis of culture-negative periprosthetic joint infections.

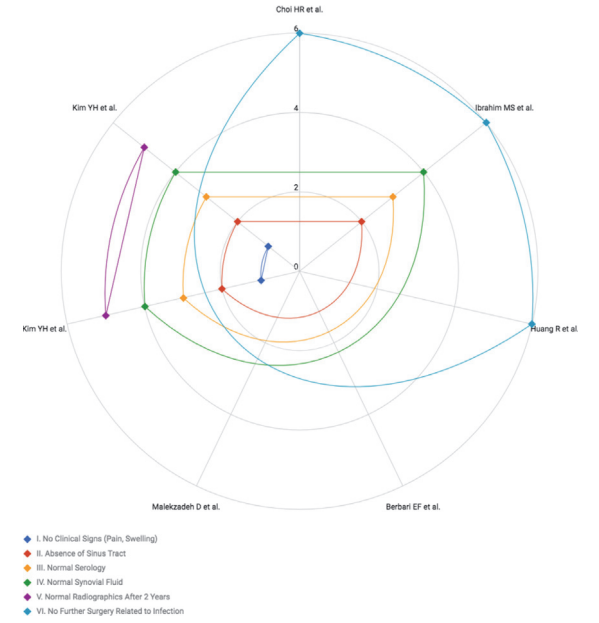

Figure 6: Definition of successful treatment.

irrigation, debridement, and retention of the prosthesis, one-stage exchange arthroplasty, or two-stage exchange of the prosthesis. The choice of the optimal treatment must be made jointly by orthopedic surgeons and experienced infectologists in accordance with the type of infection and patient's condition.

The largest amount of data in the literature is focused on the two-stage exchange arthroplasty, since this is still considered the gold standard with the lowest reinfection rates, from 0% to 36% [29, 38–44], and best functional outcomes [45–49]. But studies researching the one-stage exchange arthroplasty have also found similar reinfection rates, from 2% to 40% [27, 42, 45, 50–54]. In our systematic review most patients with culture-negative periprosthetic joint infections were treated with two-stage exchange arthroplasty, followed by 4-6 weeks of antibiotic treatment. The two-stage exchange has the highest infection-free survival rate up to 95% after five years of follow-up and a success rate ranging from 70% up to 100%. Of the included studies none recommended one-stage exchange as the first treatment option.

Table 3: Different diagnostic criteria for periprosthetic joint infections [3–13].

Parameter	MSIS criteria	AAOS	Philadelphia Consensus	Parvizi et al.	Aggarwal et al. [3]	Zimmerli et al.	Trampuz et al.	Tohtz et al. [11]	Atkins et al.	Portillo et al.	Shanmugasundaram et al. [9]	Müller et al.	Spangehl et al. [10]	Tohtz et al.	Aggarwal et al.	Shanmugasundaram et al.	Spangehl et al.	Charité (modified from Zimmerli)
Clinical																		
Sinus tract or abscess	x	x	x	x	x	x	x	x	x	x	x		x	x	x	x	x	x
Pain or poor functional status					x						x	x	x			x	x	
Erythema or swelling					x						x	x			x	x		
Pus												x	x	x	x	x	x	
Early loosening												x						
Labor																		
CRP	x (>10mg/L)		x	x (>10mg/L)	x (>10mg/L)			x (>10mg/L)				x (>0,5mg/dl)	x (>10mg/L)	x (>10mg/L)	x (>10mg/L)		x (>10mg/L)	x
ESR	x (>30mm/h)		x	x (>30mm/h)	x (>30mm/h)			x (>30mm/h)				x	x (>30mm/h)	x (>30mm/h)	x (>30mm/h)		x (>30mm/h)	x
Leucocytes								x (>10.000/ul)				x (>12.000/ul)		x (>10.000/ul)				
Histology																		
Acute infection	x	x	x	x		x	x	x	x	x	x	x	x					x
Acute infection (Type II or III according to Krenn/Morawietz)								x			x			x (>2)				
Granulocytes/HPF	x (>5)			x (>5)		x (1-10)	x (≥10)	x (≥2)	x (>5)		x (≥10)	x (≥2)	x (>5)	x (>2)		x (≥10)	x (>5)	
Microbiology																		
≥2 culture-positive samples	x	x	x	x		x	x	x	x (≥3)	x	x	x		x		x	x	x
1 culture-positive sample	x		x	x			x						x				x	x
1 culture-positive sample (high virulent germ)		x																x
Sonication																		
≥ 50 colonies/ml																		
Synovial flood																		
Leucocytes	x (>1.100 cells/ul)		x	x (>1.100 cells/ul)	x	x (>1.700 cells/ul)	x (>1.700 cells/ul)			x (>1.700 cells/ul)					x			x
Granulocytes	x (>64%)		x	x (>64%)	x	x (>65%))	x (>65%))			x (>65%))					x			x
Pus	x	x		x	x	x		x	x	x	x	x	x			x		x
Culture positive		x		x	x		x					x	x		x		x	
Main criteria																		
Secondary criteria																		

Table 4: Diagnostic parameters for CN PJI [23].

Test	Criteria	Sensitivity	Specificity
Clinical features	Sinus tract (fistula) **or** purulence around prosthesis[a]	20-30%	100%
Leukocyte count in synovial fluid[b]	>2000/ul leucocytes **or** >70% granulocytes (PMN)	≈90%	≈95%
Periprosthetic tissue histology[c]	Inflammation (≥23 granulocytes per 10 high-power fields)	73%	95%
Microbiology	Microbial growth in: (i) synovial fluid or (ii) ≥2 tissue samples[d] or (iii) sonication fluid (>50 CFU/ml)[e]	45-75% 60-80% 80-90%	95% 92% 95%

[a]Metal-on-metal bearing components can simulate pus (≪pseudopus≫), leukocyte count is usually normal (visible is metal debris)

[b]Leukocyte count can be high without infection in the first 6 weeks after surgery, in rheumatic joint disease (including crystalopathy), periprosthetic fracture or luxation.

Leukocyte count should be determined within 24 h after aspiration by microscopy or automated counter; clotted specimens are treated with 10 μl hyaluronidase

[c]Classification after Krenn and Morawietz: PJI corresponds to type 2 or type 3

[d]For highly virulent organisms (e.g. *S. aureus*, streptococci, *E. coli*) or patients under antibiotics, already one positive sample confirms infection

[e]Under antibiotics, for *S. aureus* and anaerobes, <50 CFU/ml can be significant

Table 5: Antimicrobial treatment in CN PJI [23].

Microorganism (red: difficult-to-treat)	**Antibiotic**[a] (check pathogen susceptibility before)	**Dose**[b] (italic font: *renal adjustment needed*)	**Route**
Culture-negative	Ampicillin/sulbactam[c]	*3 × 3 g*	i.v.
	for 2 weeks, followed by:		
	Rifampin[d] + Levofloxacin	2 × 450 mg	p.o.
		2 × 500 mg	p.o.

[a]**Total duration** of therapy: **12 weeks**, usually 2 weeks intravenously, followed by oral route.

[b]Laboratory testing 2x weekly: leukocytes, CRP, creatinine/eGFR, liver enzymes (AST/SGOT and ALT/SGPT). Dose-adjustment according to *renal function* and body weight (<40/> 100kg).

[c]**Penicillin allergy** of NON-type 1 (e.g., skin rash): cefazolin (3 × 2 g i.v.). In case of anaphylaxis (= type 1 allergy such as Quincke's edema, bronchospasm, and anaphylactic shock) or cephalosporin allergy, vancomycin (2 × 1 g i.v.) or daptomycin (1 × 8 mg/kg i.v.).

Ampicillin/sulbactam is equivalent to amoxicillin/clavulanic acid (3 × 2.2 g i.v.).

[d]**Rifampin** is administered only after the new prosthesis is implanted. Add it already to intravenous treatment as soon as wounds are dry and drains removed; in patients aged >75 years, rifampin is reduced to 2 × 300 mg p.o.

The included studies used different parameters to define a successful treatment. To evaluate and compare the outcome after treatment, a consistent definition of a successful treatment should be determined to enable a reliable comparison between different studies and treatment options.

As was the case regarding the surgical treatment of PJI, there is no consensus in the literature about a standardized protocol for antibiotic usage, especially not in CN PJI. Vancomycin was the antibiotic used to treat most of the patients in our included studies after surgery, either alone or in combination with other antibiotics. Choi et al. reported that high-dosage vancomycin has a better outcome in CN PJI. The rising usage of vancomycin in culture-negative infections may also be encouraged by an increasing number of MRSA infections [13]. Besides the antibiotic agent, the duration of parental and oral antibiotic treatment is another uncertain topic in the published literature, and no treatment protocol has yet been established. Trampuz et al. therefore developed a antimicrobial treatment based on international references [23] (Table 5).

Our systematic review has several limitations. First of all, the included studies are based on level III evidence and retrospective in design, which leads to a limited validity of the results of our study. Secondly, only studies published in English or German were selected, resulting in a selective presentation of included studies and results. Only eight studies that met all inclusion criteria were assessed. This led to a small sample size of patients, resulting in restricted validity of our findings. Furthermore, this only allowed us to perform a descriptive analysis of the data. Due to the small sample size, statistical methods used in the meta-analysis to summarize the results are statistically insignificant. With a low heterogeneity in the incidence rates provided by the studies we included, referral bias possibly affects the results. The possibility of not having retrieved all relevant information published on CN PJI should also be considered as one of the limitations of our study. Further, due to the lack of literature which deals with CN PJI and because of publications focusing only on positive results treating CN PJI, a publication bias is likely. Additionally, the included

studies did not utilize a standardized treatment protocol (e.g., different surgeons and operative standards, interval between stages, spacer, antibiotic treatment, and duration), which made a direct comparison of their results difficult. The descriptive analysis could not address the functional status after treatment in the selected studies because of missing information in the primary studies.

When the microorganism is confirmed, treatment outcomes are well documented in the literature. However, treatment outcome of culture-negative PJI is only reported in a few studies. In all eight studies included in this systematic review, the clinical outcome and infection control rates are similar to CP PJI groups or have even higher rates of successful treatments [16]. At the same time, when assessing the treatment success of CN PJI, one should consider the relatively short follow-up of the included studies.

Also one of the recently published articles comparing the outcome of culture-negative to culture-positive periprosthetic joint infections Kang et al. came to the conclusion that CN PJI can be treated successfully and can even show a better outcome regarding clinical course [55].

In conclusion, a culture-negative status may not be a negative prognostic factor for treatment outcome. One clearly significant factor is the appropriate selection of the surgical and antimicrobial treatment according to the type of infection, including additional factors like comorbidities, status of the patient, and operative risk for the patient. To increase the validity of the conclusions in further studies, prospectively designed studies of culture-negative PJI should implement a standardized diagnostic protocol and evidence-based treatment strategies for culture-negative periprosthetic joint infections. This will significantly increase the commensurability and thus yield more tangible recommendations.

Appendix

See Table 1 and Figure 4.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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Research Article

The Preoperative Microbial Detection is No Prerequisite for the Indication of Septic Revision in Cases of Suspected Periprosthetic Joint Infection

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Aim of This Study. Periprosthetic joint infections (PJIs) require a special antimicrobial regimen, fundamentally different from an aseptic treatment, making a correct preoperative diagnosis essential. However, a successful preoperative microbe detection is not always possible. We wanted to find out **(1)** if a preoperative microbe detection is a prerequisite before starting a septic revision in suspected PJIs or if the preoperative diagnosis can solely be based on (para)clinical signs (persistent CRP >1 mg/dl, early X-ray loosening signs in the first 5 years, leucocytes joint aspiration >1700/μl, conspicuous history, and clinical signs like redness, pain, hyperthermia, swelling, and loss of function); **(2)** if patients with and without preoperative microbe detection have a different outcome; and **(3)** if the microbial growth is the most important criterion of a multifactorial PJI definition. *Methods*. We included all first-line two-stage hip (49) and knee (47) revisions, performed in our department from 06/2013 on, with an available 2-year follow-up. A PJI was defined as one of the following four criteria: fistula or purulence, Krenn Morawietz type 2 or 3, joint aspirate > 2000/μl leukocytes or >70% granulocytes, and microbial growth. This multifactorial PJI definition was based on the European Bone and Joint Infection Society (EBJIS). The standardized diagnostic algorithm is described in detail. *Results*. **(1)** 24 hip and 16 knee cases were treated without preoperative microbe detection solely on the basis of a (para)clinical diagnosis (see above). In the hip 91.6% (22 of 24 cases) showed an intraoperative microbe detection. In the knee, in 68.7% (11 of 16 cases) a microbe was detected intraoperatively and in 93.7% (15 of 16) at least one secure PJI criterion could be confirmed intraoperatively. **(2)** No statistical significant (p .517) difference between patients with (n = 56, reinfection rate 8.9%) and without (n = 40, 15%) preoperative microbe detection was found in a 2-year follow-up. **(3)** Microbial growth remains the overall (pre- and intraoperatively) most important criterion (hip 95.9%; knee 89.3%), followed by Krenn Morawietz for the intraoperative diagnosis (hip 67.3%, knee 48.9%), and joint aspiration for the knee and fistula for the hip, respectively, as preoperative criteria. *Conclusion*. High rates of intraoperatively fulfilled EBJIS PJI criteria show that a preoperative microbe detection is not necessary before intervening in suspected PJIs. The indication for a septic revision can solely be based on (para)clinical signs. The new established diagnostic algorithm based on a multifactorial PJI definition showed high precision in finding PJIs.

1. Background and Aim of This Study

Periprosthetic joint infections (PJIs) are one of the most challenging complications in total joint arthroplasty. Their treatment requires a specific therapy protocol, essential for a successful infection free outcome and fundamentally different from an aseptic procedure [1]. This makes an accurate preoperative diagnosis essential. Frequently, a preoperative evidence of microbiological growth is required for the indication of infection therapy, arguing that germ detection is the most secure differentiation between an aseptic and septic condition (e.g., loosening). On the one hand overlooking of low-grade infections and false negative diagnosis as aseptic should be avoided by a preoperative microbe detection;

on the other hand, an unnecessary specific PJI-treatment (including antibiotics) should be prevented in cases without an actual PJI.

Unfortunately, a preoperative microbe detection is not always reliable, useful, and/or practicable, especially in the case of low-grade infections. A microbial growth via synovial fluid out of a preoperative punctuation has a sensitivity of 45-75% and a specificity of 95% [1, 2]. This means that up to 25-55% of all existing PJIs are not found and about 5% of all detected infections can be considered false positive, making the preoperative detection not always reliable. In cases of a known preoperative antibiotic therapy, a joint aspiration is additionally not useful [3]. Finally, a preoperative microbe detection is not always practicable, because of often lacking hospital capacities, and when delaying the start of an obviously necessary revision (e.g., severe pain, acute joint dysfunction, and septic shock). The pathogenic background of the aggravated preoperative diagnosis in general is a biofilm formation, especially in chronic PJI cases, covering the prosthesis surface and protecting the bacteria from being aspirated [4].

Due to all those reasons, we believe that a preoperative microbe detection should not be a compellingly necessary precondition when intervening, with a combined antimicrobial and surgical regimen, in suspected PJIs.

(1) We would like to demonstrate that the indication for septic revision can only be made on the basis of clinical and (para)clinical abnormalities, that no preoperative proof of germs is necessary, and that the final definitive diagnosis via microbe detection or another secure PJI defining criterion can be made intra/postoperatively.

(2) Additionally, we would like to find out if patients with a preoperative microbe detection might have a different outcome compared to patients without a preoperatively known microbe. We therefore analyzed the reinfection rate of those two groups in a 2-year follow-up.

(3) Finally, we would like to analyze which PJI definition criterion (clinical, histology, joint aspiration, and microbial growth) of a new multifactorial definition was the most often confirmed in the pre- and intraoperative diagnosis.

2. Methods

2.1. Inclusion/Exclusion Criteria. We performed this study on the example of the two-stage exchange as the most prevalent treatment type used in (suspected) PJIs at our department. Except two operations with a short interval (2 weeks), all included cases had a long interval (6-8 weeks) between prosthesis explanation and reimplantation. In the knee, a temporary arthrodesis, in the hip a girdlestone situation without a spacer was preferred after explanation.

We included all patients: (1) with a suspected PJI, (2) of a total hip/knee arthroplasty (THA, TKA) and/or hip hemiarthroplasty, (3) which received a two-stage exchange as a first-line treatment in our department, and (4) from 06/2013 on with an available 2-year follow-up.

We excluded all patients not treated completely in our hospital (e.g., prosthesis explanation in a different hospital).

2.2. Analysis. The data were collected retrospectively using our electronic data system (SAP). The statistical evaluation was performed using SPSS. $P < .05$ was considered as significant and Fisher exact test was used to determine significant differences between groups.

Of the included two-stage revisions, we worked out all cases without a preoperative microbe detection and a treatment indication based only on (para)clinical signs, of which at least 2 had to be positive [5]: (1) persistent CRP-value >1 mg/dl, (2) loosening signs in the X-ray (early loosening in the first 5 years), (3) leucocytes count >1700/μl in joint aspiration, (4) conspicuous history (PJI intervention in the past), and (5) clinical signs of an infection (redness, pain, hyperthermia, swelling, and loss of function). Afterwards, we analyzed how much percent of these patients clearly fulfilled the definition of a PJI (PJI definition see below) postoperatively (only referred to the explanation procedure, first stage) by a successfully detected microbe in an intraoperative sample and/or by another PJI defining criterion. Cases with microbes detected preoperatively by aspiration or biopsies in other hospitals were considered as known preoperative microbes as well.

We compared the reinfection rate of cases with a preoperatively detected microbe with the ones without a preoperatively detected microbe. The analyzed follow-up time was 2 years, beginning after the prosthesis reimplantation. Treatment failure/reinfection was defined as a negative Delphi-based definition of success [6]:

(i) No wound healing with fistula, drainage, or pain, with infection recurrence caused by the same organism strain

(ii) A subsequent surgical revision for infection after reimplantation. We extended the negative Delphi-based definition of success by the following reinfection signs: any PJI definition criterion (see below), persistent CRP-value >1 mg/dl, X-ray loosening signs, leucocytes count >1700/μl in joint aspiration, and clinical signs of infection like redness, pain, hyperthermia, swelling, and loss of function

(iii) PJI-related death (sepsis, necrotizing fasciitis)

Finally, we analyzed which PJI criterion of a multifactorial definition was the most often confirmed in the pre- and intraoperative diagnosis. Our PJI definition is based on the European Bone and Joint Infection Society (EBJIS) [7] and is similar to the Infectious Diseases Society of America (IDSA) [8]. The EBJIS Guidelines have been used increasingly in recent years in several outcome studies [9, 10]. They turned out to show a higher sensitivity for low-grade PJIs compared to the Musculoskeletal Infection Society (MSIS) [11, 12]. Following the EBJIS definition, a PJI is diagnosed if at least one of the following criteria is fulfilled:

(i) Clinical: sinus tract (fistula) or purulence around prosthesis

(ii) Cell count in joint aspiration: > 2000/μl leukocytes or > 70% polymorphonuclear granulocytes (PMN)

(iii) Histology: inflammation in periprosthetic tissue (type 2 or 3 after Krenn Morawietz) [13]

(iv) Microbial growth in synovial fluid or ≥ 2 tissue samples (in cases of high virulent microbes like Staph. aureus one sample is considered sufficient) or sonication fluid ≥ 50 CFU/ml

The results of the EBJIS were also briefly compared with the ones of the IDSA criteria. In contrast to the EBJIS, the IDSA only uses clinical features like sinus tract or purulence, histopathologic examination of the periprosthetic tissue, and positive microbe detection, but not the cell count in joint aspiration as definitive PJI criteria [8].

2.3. Diagnostic Algorithm. The idea of a multifactorial PJI definition is also present in the diagnosis algorithm used in our department (Figure 1). This algorithm was the basis of our preoperative diagnosis and following the idea that a preoperative microbe detection is not necessary when starting a septic revision in suspected PJIs. For example, the indication for a septic revision could be justified solely by finding a sinus tract or a suspicious leukocyte count in the joint aspiration. However, the indication for a septic revision also can be based on findings in septic patients via a preoperative microbe detection. Additionally, the algorithm puts a special emphasis on identifying the infectious focus.

3. Results

Overall, we were able to include 49 hips and 47 knee two-stage exchanges. Table 1 is showing the rates of pre- and intraoperatively detected microbes. In the hip, we were not able to identify microbes in 48.9% (24 cases) of the cases before the prosthesis explanation took place. Of these 24 cases, 91.6% (22 of 24 cases) showed an intraoperative microbe detection, 50% (12 of 24) an intraoperatively detected microbe, and additionally an infectious periprosthetic membrane (type 2 or 3 based on Krenn Morawietz classification), and in 95.8% (23 of 24 cases) at least one PJI criterion was fulfilled intraoperatively. In the knee, in 34.0% (16 of 47 cases) a microbe could not be determined preoperatively. Of these 16 cases, a microbe could be found intraoperatively in 68.7% (11 of 16 cases), in 31.2% (5 of 16) an intraoperatively detected microbe, and additionally an infectious Krenn Morawietz membrane type were identified, and in 93.7% (15 of 16 cases) at least one PJI criterion could be confirmed intraoperatively. None of the differences is significant when comparing hip and knee.

Cases with a preoperatively detected microbe are showing a lower reinfection rate after the 2-year follow-up (8.9%, 5 of 56 cases) than cases without a known preoperative microbe (15%, 6 of 40). However, this difference is not significantly higher (p .517).

Table 2 is showing the preoperatively fulfilled (para)clinical signs in suspected hip and knee PJIs. In both hip and knee, clinical signs of an infection existed in all cases. The second most important preoperatively criterion was a persistent CRP-value >1 mg/dl in 71.4% of the hip- and 63.8% of the knee infections (p .514). A prosthesis loosening in the X-ray, which is significantly (p .013) more often present in hip (53%) than in suspected knee infections (27.6%), and a conspicuous history (45% hip, 59% knee) were also relevant parameters. Leucocytes count >1700/μl in joint aspiration is the least important preoperative paraclinical sign and not showing significant differences (p .631) between hip (20.4%) and knee (25.5%).

Additionally, we analyzed the rates of pre- and intraoperatively fulfilled PJI criteria, shown in Table 3. All two-stage exchanges in the hip and 97.8% of the knee fulfilled at least one PJI criterion. Thereby, overall more PJI criteria could be confirmed intraoperatively than preoperatively in both hip (97.9%, 69.3%, p < .001) and knee (85.1%, 68.0%, p .087). The microbial growth was the overall most often fulfilled PJI criterion. In the hip 95.9% (47 of 49) and in the knee 89.3% (42 of 47) fulfilled this PJI definition either pre- or intraoperatively. Microbial detection was also the most confirmed isolated preoperative (hip 51%, knee 65.9%) and intraoperative (hip 85.7%, knee 65.9%) diagnosis criterion. The second most overall and second most intraoperatively fulfilled PJI criterion was an infectious periprosthetic membrane (Krenn Morawietz type 2 or 3). This histological PJI criterion usually only can be fulfilled intraoperatively (67.3% in the hip; 48.9% in the knee). In some cases, a preoperative diagnosis via arthroscopy is possible, too. However, this was not the case in this patient group. The third overall most fulfilled criterion (knee 44.6%; hip 30.6%) was a suspicious joint aspiration (cell count >2000/μl leukocytes or > 70% PMN). Thereby, the isolated pre- (20.4%) and intraoperative (16.3%) hip rates, as well as the isolated pre- (23.4%) and intraoperative (27.6%) knee rates, were comparable. The overall least fulfilled criterion was a sinus tract (fistula) or purulence around prosthesis (hip: 22.4%; knee 8.5%). In the hip, all preoperative known fistula could be confirmed intraoperatively (22.4%), but no other additional case with purulence around the prosthesis was identified. In the knee, one additional case fulfilling this criterion could be found intraoperatively (8.5%) compared to the preoperative situation (6.3%).

Compared with the EBJIS definition results, the IDSA criteria only considered 93 of the 96 cases as a PJI. The two further cases defined via the EBJIS criteria were solely defined via the joint aspiration as an additional criterion compared to the IDSA results. One case affected the hip, the other one the knee. Both cases had no reinfection in the 2-year follow-up and no intervention because of a PJI in the past. However, in both cases infection symptoms, in one additional loosening signs in the X-ray and in the other one a suspicious joint aspiration, were found in the preoperative situation, making the decision for intervention justified. The only case neither fulfilling one EBJIS nor one IDSA criterion was a knee joint. The patient had a septic revision in the past, showed loosening signs in the preoperative X-ray, had clinical symptoms of an infection, and had an elevated CRP >1 mg/dl.

Table 1: Rates of pre- and intraoperatively detected microbes.

Number of two-Stage exchanges	Hip	Knee	P
Total Number of two-Stage exchanges	49	47	-
Two-stage exchanges without a preoperatively detected microbe	24 (48.9%)	16 (34.0%)	.153
Two-stage exchanges without a preoperatively detected microbe, but an intraoperatively detected microbe	22 of 24 (91.6%)	11 of 16 (68.7%)	.094
Two-stage exchanges without a preoperatively detected microbe, but intraoperatively detected microbe and additionally found Krenn Morawietz type 2 or 3	12 of 24 (50%)	5 of 16 (31.2%)	.332
Two-stage exchanges without preoperatively detected microbe, but at least one intraoperatively fulfilled PJI criterion	**23 of 24 (95.8%)**	**15 of 16 (93.7%)**	**.999**

Table 2: Preoperatively fulfilled (para)clinical signs in suspected hip and knee PJIs.

Preoperative (para-)clinical signs	Hip (n = 49)	Knee (n = 47)	P
Persistent CRP-value >1 mg/dl	35 of 49 (71.4%)	30 of 47 (63.8%)	.514
Loosening signs in the X-Ray, *especially early* loosening in the first 5 years (ranging from decent loosening to entire migration)	26 of 49 (53.0%)	13 of 47 (27.6%)	.013
Leucocytes count >1700/μl in joint aspiration (Not determinable for every patient)	10 of 49 (20.4%)∗	12 of 47 (25.5%)∗	.631
Conspicuous history (PJI intervention in the past)	22 of 49 (45%)	28 of 47 (59%)	.160
≥ 1 clinical signs of an infection (redness, pain, hyperthermia, swelling, loss of function)	49 of 49 (100%)	47 of 47 (100%)	-

∗ not available for each patient.

Table 3: Rates of pre- and intraoperatively fulfilled PJI criteria, following the 4 PJI definitions of the EBJIS.

Hip, n=49	Overall (pre – or Intraoperative)	preoperative	intraoperative (explanation)
Sinus tract (fistula) or purulence	11 of 49 (22.4%)	11 of 49 (22.4%)	11 of 49 (22.4%)
>2000/μl leukocytes or >70% PMN	15 of 49 (30.6%)∗	10 of 49 (20.4%)	8 of 49 (16.3%)∗
Krenn Morawietz type 2 or 3	33 of 49 (67.3%)∗	0	33 of 49 (67.3%)∗
Microbial growth	**47of 49 (95.9%)**	**25 of 49 (51%)**	**43 of 49 (85.7%)**
At least one PJI criterion	49 of 49 (100%)	34 of 49 (69.3%)	48 of 49 (97.9%)
Knee, n=47	**Overall (pre – or Intraoperative)**	**preoperative**	**intraoperative (explanation)**
Sinus tract (fistula) or purulence	4 of 47 (8.5%)	3 of 47 (6.3%)	4 of 47 (8.5%)
>2000/μl leukocytes or >70% PMN	21 of 47 (44.6%)∗	11 of 47 (23.4%)∗	13 of 47 (27.6%)∗
Krenn Morawietz type 2 or 3	23 of 47 (48.9%)∗	0	23 of 47 (48.9%)∗
Microbial growth	**42 of 47 (89.3%)**	**31 of 47 (65.9%)**	**31 of 47 (65.9%)**
At least one PJI criterion	46 of 47 (97.8%)	32 of 47 (68.0%)	40 of 47 (85.1%)

∗ not available for each patient

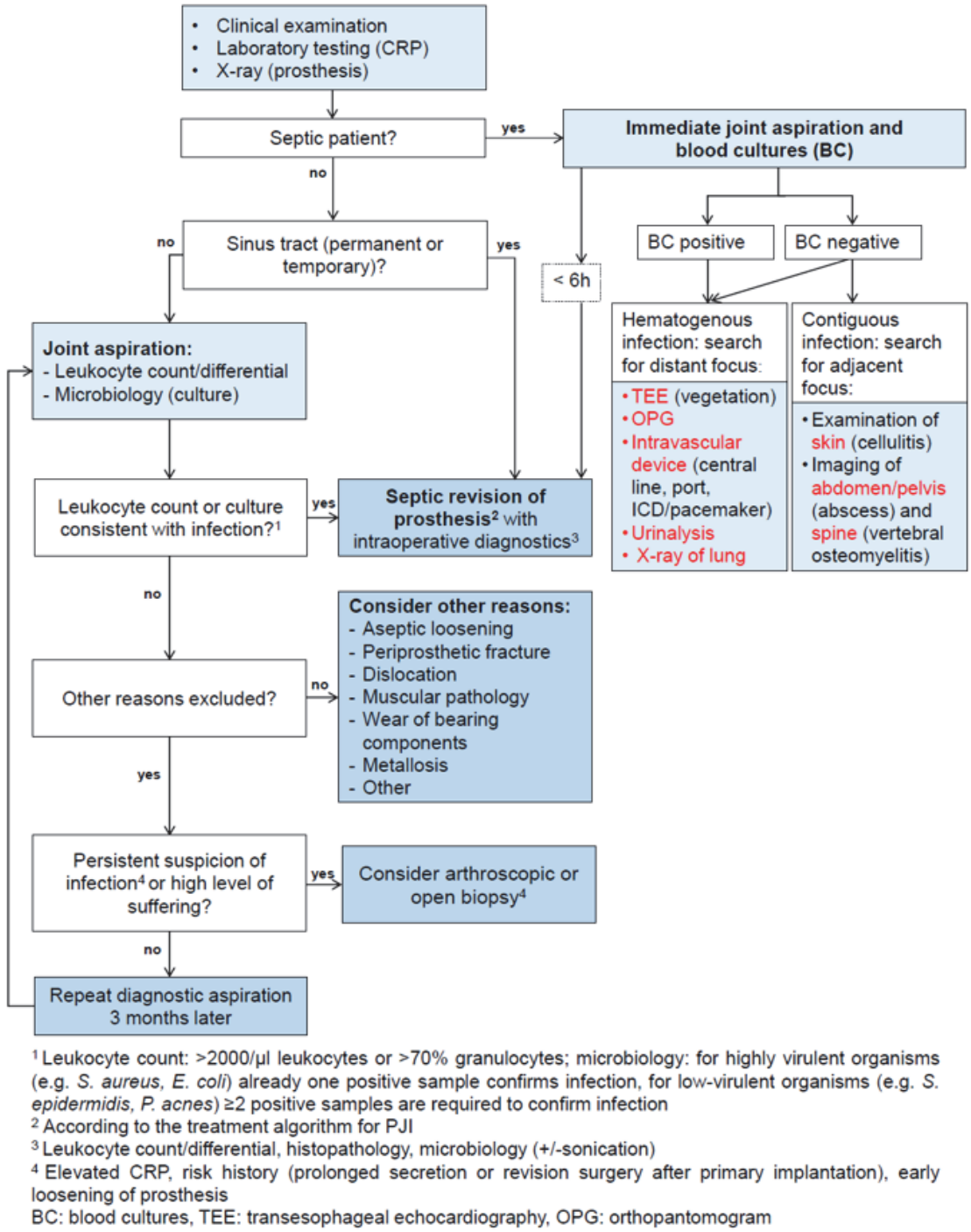

Figure 1: Diagnostic algorithm [2].

The pathologist report, after the prosthesis explanation, was neither able to identify a clear infection via Krenn Morawietz (type I), nor able to rule out an infection totally because of one nonperiprosthetic tissue sample with possible signs of a low-grade infection. The patient did not have another septic revision in the 2-year follow-up.

4. Discussion

Septic revisions without a preoperatively detected microbe are of high clinical importance. We were able to show that over a 2.5-year-long period of time, including almost 100 two-stage exchanges, almost every second hip (48.9%),

and more than every third (34.0%) knee revision, was indicated by highly clinical and paraclinical suspicion of PJI but performed without a preoperatively detected microbe. Of these operations, the rate of intraoperatively first-time detected microbes is higher in hips (91.6%) than in knee joints (68.7%). This shows that, in contrast to the hip, the intraoperative microbe detection as only PJI criterion, without preoperatively known microbe, is not sufficient for the final PJI diagnosis in knee patients. A combined diagnosis via intraoperative microbe detection (sensitivity 45-90%; specificity 92-95%) and an additionally found infectious periprosthetic membrane (Krenn Morawietz 2 or 3; sensitivity 73%; specificity 95%) is able to increase the already high sensitivity and specificity of both isolated criteria even further [1, 2]. When using this strict combined intraoperative PJI criterion, the rates in neither hip (50%) nor knee (31.2%) would be sufficient, for a septic revision in suspected PJIs, without a preoperatively known microbe. However, we consider the high rates (95.8% hip; 93.7% knee) of at least one intraoperatively found PJI criterion, in cases without preoperatively known microbe, as a sufficient proof, that the primary indication for a revision solely can be based on (para)clinical signs and that a preoperative microbe detection is no necessary prerequisite before intervening in suspected PJIs with a septic revision. The four used PJI definition criteria are showing a specify of 92-100% [1, 2] and are widely accepted as defining criteria in the EBJIS and three of them in the IDSA definition [7, 8].

The reinfection rates of cases with a preoperatively detected microbe and the ones without preoperative detection are not showing significant differences in a 2-year follow-up. However, the group with preoperative microbe detection still shows a 6.1% lower reinfection rate. Even this slightly higher rate has enormous cost for the health care system and significant clinical importance for the individual patient making an efficient and correct preoperative diagnosis a necessity [1, 14, 15]. Overall, the study shows the high importance of an efficient preoperative microbe detection. Maybe an earlier targeted and more specific antibiotic therapy might explain the different outcome. Here, further research seems promising.

Suspicious clinical presentation and a CRP-value >1 mg/dl are the most important (para)clinical PJI signs without a definitive confirmation of the diagnosis. The microbial growth remains the overall (pre- and intraoperative) most import definitive PJI criterion in hip and knee patients, followed by Krenn Morawietz for the intraoperative diagnosis, and joint aspiration for the knee, fistula for the hip respectively, as preoperative diagnosis criterion. However, microbial growth as only definitive criterion is not sufficient. It failed to include 4.1% of all hip infections and even 8.5% of all knee PJIs, defined by another criterion. This shows the necessity of a multifactorial PJI definition and diagnosis, which has also become the standard in modern guidelines like MSIS, IDSA, and EBJIS.

For a further comparison and interpretation of the different rates of fulfilled PJI criteria in hips and knees, detailed diagnosis information would be necessary, especially the absolute number of performed joint aspirations, arthroscopies, gathered tissue samples, and histology membrane samples (Krenn Morawietz). Without this information, a final comparison between single hip and knee results is not possible or useful. For example, a specific PJI criterion rate can be higher in one joint type because of a more intense diagnosis (e.g., more preoperative arthroscopies in knee PJIs could lead to a higher preoperative rate of the microbial growth criterion), while in other criteria structural differences might explain the results. However, such a detailed comparison was not the aim of this study. We wanted to analyze which PJI criterion was the most important in a daily clinical routine, under consideration of different diagnostic intensity. As only criterion, further diagnosis information is not necessary, when evaluating the clinical definition (fistula, purulence). This criterion is primarily a first view diagnosis and thus not showing major differences in the level of diagnosis. Here, higher rates could be found in hip PJIs (p .091). This could be explained by the fact that the hip is a larger joint, making a clinical view diagnosis (fistula, purulence) easier.

In the last years, a general preference towards algorithm systems for the diagnosis of PJIs could be seen. The developed algorithms vary, depending on their setting and aim. Some algorithms focus on hospitals without specialization on PJIs and present systems with as few steps as possible [17], while others put a stronger focus on maximal precision in a scientific analysis and research context [18]. Our diagnostic algorithm is showing high accuracy in finding PJIs. All two-stage exchange operations in the hip and 97.8% of the knee fulfilled at least one PJI criterion.

5. Conclusion

A preoperative microbe detection is not necessary before intervening in suspected PJIs. The indication for a septic revision can solely be based on clinical and paraclinical signs (persistent CRP-value > 1 mg/dl, conspicuous history, loosening signs in the X-ray, early loosening in the first 5 years, leucocytes count >1700/μl in joint aspiration, and clinical signs). Thereby, suspicious clinical presentation and a CRP-value >1 mg/dl are still the most important (para)clinical signs. Cases with a preoperatively detected microbe are showing slightly better results compared to cases without a known preoperative microbe. The pre- and intraoperative microbe detection remains the most import PJI definition and diagnosis criterion. Our new established diagnostic algorithm is showing high accuracy in finding PJIs. However, a detailed analysis of the algorithm will be necessary for a final evaluation. Overall, the results found in this study might be helpful when making future decisions in unclear preoperative situations.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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Clinical Study

Synovial Fluid Aspiration Should Not Be Routinely Performed during the Two-Stage Exchange of the Knee

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Purpose. Detection of infection persistence during the two-stage exchange of the knee for periprosthetic joint infection is challenging. Synovial fluid culture (SFC) and synovial white blood cell count (SWBCC) before joint reimplantation are widespread diagnostic means for this indication. The sensitivity and specificity of SFC and of SWBCC for infection persistence before planned reimplantation were evaluated. *Methods*. 94 two-stage exchanges of the knee with synovial fluid aspiration performed after a drug holiday of at least 14 days and before reimplantation or spacer exchange (planned reimplantation) were retrospectively analyzed. Only cases with at least 3 intraoperative samples at planned reimplantation were included. SFC and SWBCC were compared to pathogen detection ($SFC_{(culture)}$/$SWBCC_{(culture)}$) and to histopathological signs of infection persistence ($SFC_{(histo)}$/$SWBCC_{(histo)}$) from intraoperative samples at planned reimplantation. For SFC, the sensitivity and specificity were calculated. For SWBCC, the optimal cut-off value with its sensitivity and specificity was calculated with the Youden-Index. *Results*. Sensitivity and specificity of $SFC_{(culture)}$ were 0.0% and 98.9%. Sensitivity and specificity of $SFC_{(histo)}$ were 3.4% and 100%. The optimal cut-off value for $SWBCC_{(culture)}$ was 4450 cells/μl with a sensitivity of 50.0% and a specificity of 86.5%. The optimal cut-off value for $SWBCC_{(histo)}$ was 3250 cells/μl with a sensitivity of 35.7% and a specificity of 92.9%. *Conclusion*. The detection of infection persistence remains challenging and a consented approach is lacking. The results do not warrant the routine performance of SFC during the two-stage exchange at the knee. SWBCC can be used to confirm infection persistence at high cut-offs, but they only occur in few patients and are therefore inappropriate for the routine use.

1. Introduction

Periprosthetic joint infection (PJI) is a devastating complication after total knee arthroplasty (TKA). Although the risk of PJI after primary TKA is reported as low as 0.5% to 1.9% [1], between 14.8% and 25.0% of TKA revisions are performed because of PJI [2–5]. With the expected increase of primary TKA, the absolute number of PJI will increase, too [6]. The two-stage exchange (TSE) is the most preferred treatment for PJI of the knee [1, 7]. The first stage of the TSE consists of prosthesis removal along with debridement of all infected tissue and commonly implantation of an antibiotic-loaded spacer. The first stage is followed by systemic antibiotic administration. At the second stage, a prosthesis is reimplanted or, in cases of infection persistence, the joint is redebrided, the spacer exchanged, and another course of systemic antibiotics administered. Infection persistence is assessed by means of clinical examination and blood infection markers such as the C-reactive protein (CRP). Synovial fluid culture (SFC) and synovial white blood cell count (SWBCC) gained from the affected joint by aspiration before the planned reimplantation (interstage aspiration (IA)) ought to help discriminating infection persistence from infection eradication. This evaluation of infection eradication with cultures from the joint before planned reimplantation is a well-established treatment algorithm [8]. Since the continuous administration of antibiotics until aspiration has been shown to reduce culture sensitivity of the SFC [9], an antibiotic free interval before IA, the so-called drug holiday, is recommended [1]. However, because of the drug holiday and

the time until final results of the SFC are available, IA extends the duration until the second stage can be performed. A shorter interval to planned reimplantation may decrease soft tissue contraction, shorten immobilisation, and ultimately improve quality of life [10]. Thus, the routine implementation of the IA into the TSE has regained controversy [11], especially since recent studies showed a questionable clinical value.

Hoell et al. reported a sensitivity of the SFC by IA at hips and knees of only 5.0% [12]. Recent studies from hips with a girdlestone situation or with an indwelling spacer have confirmed this poor result with sensitivities between 4.3% and 30.0% [13, 14]. The study by Lonner et al. reported a sensitivity of 0.0% in 2001 from 34 TSEs of the knee [15].

Next to the SFC, the SWBCC may help to rule out infection persistence. However, derived from studies of the hip and studies of knees and hips, the optimal cut-off during the TSE is unclear and ranges between 640 and 2000 cells/μl [12, 14, 16].

This study investigates the sensitivity of the SFC for infection persistence during the TSE at the knee under microbiological and histopathological considerations. Additionally, this is the first study to analyze the cut-off values of the SWBCC particularly at the knee.

2. Methods

2.1. Patient Inclusion. After approval by the institution's ethics review board, the electronic database of our orthopaedic department was retrospectively searched for all TSEs of the knee done between 12/07 and 06/17 (N=322). From these, 5 patients died before the second stage and further 5 denied reimplantation. 10 patients were excluded because primary TKA was done after tumor resection. 54 TSEs were excluded because IA was not performed. 51 TSEs were excluded because the drug holiday was less than 14 days. PJI was retrospectively defined according to the Clinical Practice Guidelines by the Infectious Disease Society of America as (a) sinus tract that communicates with the prosthesis; (b) presence of acute inflammation as seen on histopathologic examination of periprosthetic tissue at the time of prosthesis removal; (c) presence of purulence around the prosthesis; (d) two or more intraoperative cultures or combination of preoperative aspiration and intraoperative cultures that yield the same organism/or the growth of Staphylococcus aureus in a single specimen of synovial fluid or a tissue biopsy [7]. For this PJI definition further 55 cases had to be excluded. Finally, 48 TSEs were excluded because less than 3 intraoperative samples for microbiological evaluation were collected at the second stage, leaving 94 TSEs for analysis (Figure 1).

2.2. Treatment Regimen. Stage one of the TSE consisted of the removal of the prosthesis and debridement of infectious altered tissue and bone. In dependence of the soft tissue and bony situation an articulating or a static antibiotic-loaded polymethylmethacrylate spacer was implanted. The spacer was hand molded around Steinman spins as an endoskeleton from Palacos® R+G (Fa. Heraeus, Germany), a gentamicin premixed bone cement. 2 grams of vancomycin was additionally added per 40 cc batch of the bone cement. Antibiotics were administered for 4 to 8 weeks in dependence of pathogen detection and as recommended by the infectious specialist. Before this study, IA was performed by default after a drug holiday of 2 weeks under sterile conditions in an operating theater. After samples for the SFC were obtained, the remaining synovia was used for the SWBCC. If the SFC yielded no growth after 16 days of cultivation and the course of the CRP as well as clinical examination showed no persisting infection reimplantation was performed. Otherwise the spacer was exchanged. After reimplantation antibiotic treatment was continued for two weeks if tissue samples remained sterile. In case of pathogen detection antibiotic treatment was extended for 6 weeks as recommended by the infectious specialist.

2.3. Definitions and Statistics. Infection persistence was defined by microbiological and histopathological findings at planned reimplantation.

For infection persistence under a microbiological aspect, the SFC at IA was considered true positive, if it yielded the same pathogen detected from the intraoperative tissue samples at planned reimplantation ($SFC_{(culture)}$). The $SFC_{(culture)}$ was considered true negative, if it remained sterile and the intraoperative samples from planned reimplantation yielded less than two identical pathogens. The $SFC_{(culture)}$ was considered false negative, if it remained sterile, but a virulent microorganism such as Staphylococcus aureus or Pseudomonas aeruginosa grew from at least one intraoperative tissue sample or a nonvirulent microorganism from at least two. These definitions are in accordance with the current recommendations by the Infectious Disease Society of America and Musculoskeletal Infectious Society [7, 17]. The SWBCC was considered true positive, if it was above the cut-off level and at least two intraoperative tissue samples yielded the same pathogen or one sample a virulent pathogen ($SWBCC_{(culture)}$).

For infection persistence under a histopathological aspect, the SFC at IA was considered true positive, if it yielded a pathogen and intraoperative tissue samples at planned reimplantation showed histopathologic signs of infection ($SFC_{(histo)}$). The SWBCC was considered true positive, if it was above the cut-off level and intraoperative tissue samples at planned reimplantation showed histopathologic infection persistence ($SWBCC_{(histo)}$). Tissue samples showing acute inflammation as recommended by the Infectious Disease Society of America guideline [7] or periprosthetic membranes classified as type II or III according to Krenn and Morawietz [18] were regarded as infection persistence.

Sensitivity was defined as the number of true positive specimens/(true positive + false negative specimens), specificity as the number of true negative specimens/(true negative + false positive specimens), positive predictive value as the number of true positive specimens/(true positive + false positive specimens), and negative predictive value as the number of true negative specimens/(true negative + false negative specimens). Means were compared with the Mann–Whitney U test. $P < 0.05$ was set statistically significant.

The optimal cut-off value for the SWBCCs was calculated with the Youden-Index after performing a receiver operating

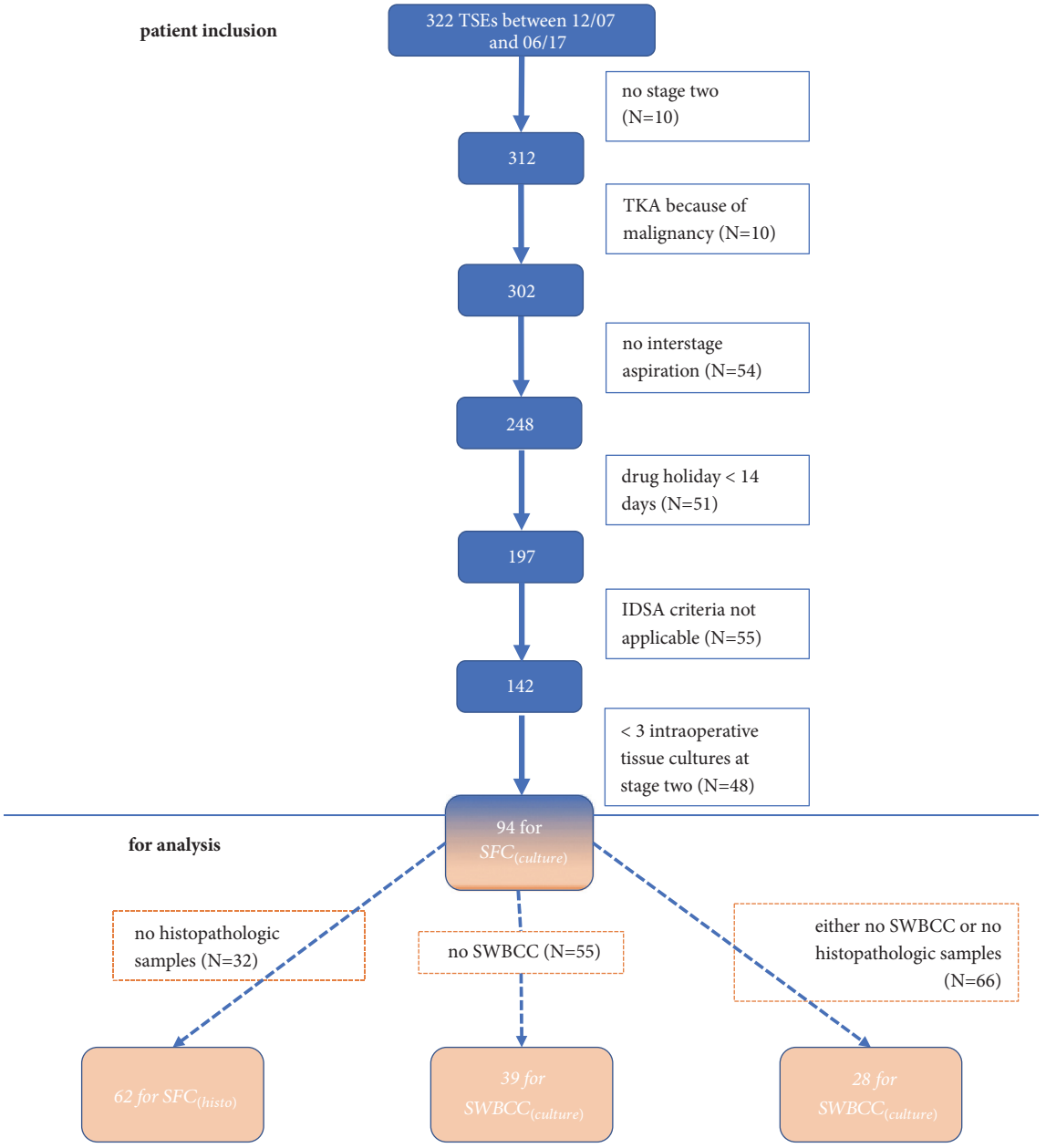

Figure 1: Flow chart of patient inclusion and numbers for analysis. TSE: two-stage exchange; TKA: total knee arthroplasty; IDSA: Infectious Disease Society of America; SFC: synovial fluid culture; SWBCC: synovial white blood cell count.

characteristics curve. All statistics were conducted with SPSS version 23 (SPSS Inc. Chicago, IL, USA).

3. Results

3.1. Patients and Treatment. 94 TSEs were included. The mean duration from index surgery to prosthesis removal and spacer implantation was 46.8 months (1 – 192) with 61.7% of the TSEs being repeated revisions. 47.9% were male patients. Mean age at TSE was 69.0 years (46 – 91) and the mean BMI was 31.0 kg/cm^2 (20.5 – 48.1). Pathogens identified at PJI diagnosis are depicted in Table 1.

An articulating spacer was implanted in 75.5 % and a static spacer in 24.5%. The mean duration of intravenous antibiotic administration was 16.3 days (8 – 38) followed by a course of oral antibiotic therapy for a mean of 16.9 days (3 – 31). The mean drug holiday was 18.0 days (14 – 48). The mean duration from prosthesis removal to planned reimplantation was 74.0 days (54 – 147). Mean CRP before stage two was 1.1 mg/dl (0.00 – 10.00). In 6 patients, a spacer exchange was performed as second stage, in two because of intraoperative aspect of purulence, in one because of detection of Staphylococcus hominis at IA, and in 3 because of suspicious course of the CRP. 3.1 (3 – 4) microbiologic samples were taken at planned reimplantation.

Table 1: Pathogens detected at diagnosis of periprosthetic infection.

Pathogen	N (%)
Staphylococcus epidermidis	19 (20.21)
Staphylococcus aureus	15 (16.00)
Other CNS	13 (13.83)
Streptococci	5 (5.32)
Corynebacterium spp.	1 (1.1)
Escherichia coli	1 (1.1)
Enterobacter cloacae	1 (1.1)
Enterococcus faecalis	1 (1.1)
Bacillus cereus	1 (1.1)
Micrococcus luteus	1 (1.1)
Moraxella osloensis	1 (1.1)
MRSA	1 (1.1)
Cutibacterium acnes	1 (1.1)
Pseudomonas aeruginosa	1 (1.1)
Rothia dentocariosa	1 (1.1)
Polymicrobial	8 (8.51)
Culture-negative	23 (24.47)

CNS: coagulase negative staphylococci; MRSA: multi-resistant Staphylococcus aureus.

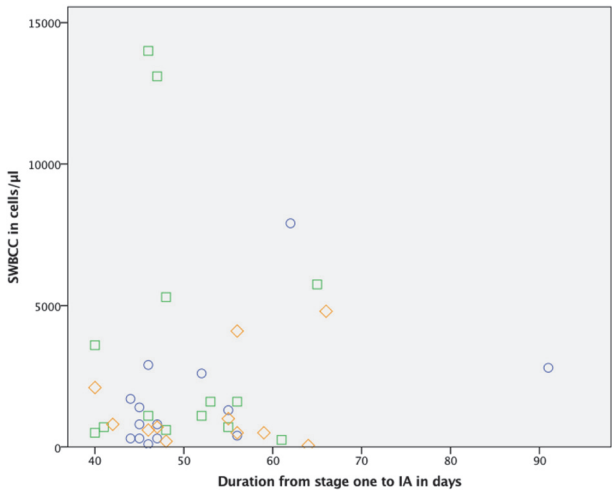

Figure 2: Correlation between synovial white blood cell count and duration from stage one to interstage aspiration. SWBCC: synovial white blood cell count; IA: interstage aspiration; circles showing SWBCC without histopathologic samples indicating infection persistence; squares showing SWBCC with histopathologic samples indicating infection persistence; diamonds showing SWBCC without histopathologic samples.

3.2. Synovial Fluid Cultures from IA Compared to Microbiological Samples at Planned Reimplantation ($SFC_{(culture)}$). 88 SFCs were true negative with sterile results from IA and the second stage. Further 3 sterile SFCs were considered true negative, although Staphylococcus epidermidis was cultivated from one single intraoperative sample. Microbiological infection persistence at reimplantation occurred in two cases: Staphylococcus epidermidis was cultured in 2 of 4 samples in the first and Staphylococcus epidermidis together with Pseudomonas aeruginosa from one of three samples in the second case. In both patients, the SFC was false negative. One SFC was false positive with growth of Staphylococcus hominis, but sterile samples at spacer exchange. The sensitivity of the $SFC_{(culture)}$ was 0.0% (Table 2).

3.3. Synovial Fluid Cultures from IA Compared to Histopathologic Samples at Planned Reimplantation ($SFC_{(histo)}$). Histopathologic samples from the planned reimplantation were available in 62 TSEs. In 29 cases, tissue samples showed infection persistence (positive). In one of these cases, the SFC yielded a pathogen, which was Staphylococcus hominins (true positive). In the remaining 33 cases tissue samples showed no infection persistence and the SFCs were negative (true negative).

3.4. Synovial White Blood Cell Count at IA Compared to Microbiological Samples at Planned Reimplantation ($SWBCC_{(culture)}$). SWBCC results from 39 TSEs were available. The two cases with microbiological infection persistence had SWBCCs of 4800/μl and of 600/μl (positive). In one patient with a SWBCC of 500/μl at IA one of three tissue cultures at planned reimplantation yielded Staphylococcus epidermidis (negative). The remaining 36 cases with a mean SWBCC of 2304/μl (50 – 14000) had sterile tissue cultures at planned reimplantation (negative). The threshold with the highest Youden-Index (0.365) was 4450/μl with a sensitivity of 50% and a specificity of 86.5%.

3.5. Synovial White Blood Cell Count from IA Compared to Histopathologic Samples at Planned Reimplantation ($SWBCC_{(histo)}$). There was no correlation between the SWBCC and the duration from stage one to IA as shown in Figure 2. SWBCCs with the corresponding histopathologic samples from planned reimplantation were available in 28 cases.

In the 14 cases with histopathologic infection persistence the mean SWBCC was 3564/μl (250 – 14000). Of these, one case yielded Staphylococcus epidermidis in one of three tissue cultures at reimplantation. The SWBCC was 600/μl. In the remaining 14 cases without histopathologic infection persistence the mean SWBCC was 1686/μl (100 – 7900). None of these cases had pathogen detection at planned reimplantation. We found no significant difference between SWBCCs with infection persistence or with infection eradication (p=0.329).

The SWBCC cut-off with the highest Youden-Index was 3250/μl with a sensitivity of 35.7% and a specificity of 92.9% as shown in Table 3.

4. Discussion

We found insufficient sensitivity of the SFC for the routine performance during TSE in order to detect infection persistence. The high threshold of $SWBCC_{(culture)}$ 4450/μl had specificity of 86.5% but with a sensitivity of only 50%.

In spite of the retrospective design, the strengths of this study are the high number of cases, the strict adherence to the drug holiday, the sampling of at least three tissue specimens

Table 2: Sensitivity and specificity of synovial fluid culture and synovial leukocyte count at interstage aspiration.

	Threshold	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
$SFC_{(culture)}$	culture positive	0.000	0.989	0.000	0.978
$SFC_{(histo)}$	culture positive	0.034	1.000	1.000	0.541
$SWBCC_{(culture)}$	4450 cells/μl	0.50	0.865	0.167	0.970
$SWBCC_{(histo)}$	3250 cells/μl	0.357	0.929	0.833	0.591

SFC: synovial fluid culture; SWBCC: synovial white blood cell count.

Table 3: Youden-Index in relation to synovial cell count with sensitivity and specificity for histopathologic infection persistence.

Youden-Index	SWBCC (cells/μl)	Sensitivity	Specificity
0.000	99	1.000	0.000
0.071	175	1.000	0.071
0.000	275	0.929	0.071
0.214	350	0.929	0.286
0.286	450	0.929	0.357
0.214	550	0.857	0.357
0.143	650	0.786	0.357
0.000	750	0.643	0.357
0.143	950	0.643	0.500
0.000	1200	0.500	0.500
0.071	1350	0.500	0.571
0.143	1500	0.500	0.643
0.000	1650	0.357	0.643
0.071	2150	0.357	0.714
0.143	2700	0.357	0.786
0.214	2850	0.357	0.857
0.286	***3250***	***0.357***	***0.929***
0.214	4450	0.286	0.929
0.143	5525	0.214	0.929
0.071	6825	0.143	0.929
0.143	10500	0.143	1.000
0.071	13550	0.071	1.000
0.000	14000	0.000	1.000

SWBCC: synovial white blood cell count.

for culture at planned reimplantation as recommended by the Infectious Disease Society of America and Musculoskeletal Infectious Society, and the clear definition of infection persistence. However, several limitations need to be discussed.

So far, there is no uniform definition of infection persistence during the TSE. In the current study, infection persistence was defined under two different aspects: pathogen detection and histopathologic evaluation. As a clear limitation to this study, other features, that might indicate infection persistence such as pus and the CRP, were not considered. Newman et al. determined modified Musculoskeletal Infectious Society criteria for the definition of infection persistence at the hip [14]. Although only a small proportion of cases was diagnosed on the bases of minor criteria, it should be mentioned that the values of purulence or of the CRP as indicators for infection persistence have not been ultimately determined and remain controversial [11, 12, 19]. Additionally, more complex infection persistence definitions bear the risk of lacking traceability [13, 15]. In accordance with other authors, we defined infection persistence as detection of the same pathogen in at least two intraoperative cultures or detection of a virulent pathogen in a single [12, 16, 20]. But still, derived from the results of PJI diagnosis, infection can occur without pathogen detection in up to 24% [21]. As an alternate tool for PJI diagnosis [10, 22], histopathological evaluation was also investigated. In accordance with $SFC_{(culture)}$ the sensitivities of $SFC_{(histo)}$ and $SWBCC_{(histo)}$ were very low, too. However, we noted a low consistency of cultures and histopathologic results at planned reimplantation. Only 6.9% of the cases with histopathologic infection persistence yielded a pathogen. Both these cases were Staphylococcus epidermidis in one of three intraoperative tissue cultures. Accordingly, the only culture positive IA was considered false positive for $SFC_{(culture)}$ and true positive

Table 4: Comparison of results for sensitivity and specificity for interstage aspiration by different authors.

Author	Definition of persistent infection	Joints	SFC		SWBCC		
			Sensitivity	Specificity	Cut-off	Sensitivity	Specificity
Hoell et al. 2016	at least two identical tissue cultures at SES	56 Hip- and 59 Knee-Spacers	0.05	0.99	970	0.313	0.391
Newman et al. 2017	modified MSIS at SES	77 Hip-Spacers	0.30	1.00	1166	0.76	0.78
Zmistowski et al. 2017	positive tissue culture at SES, and/or subsequent surgery for PJI after reimplantation	40 Hip- and 88 Knee-Spacers	-	-	1234	0.444	0.755
Muhlhofer et al. 2018	2 positive tissue cultures at SES	92 Hip- and Knee- Spacers (60 for SWBCC)	0.06	0.92	-	0.10	0.81
Boelch et al. 2018	modified IDSA criteria at SES	92 Hip-Spacers	0.05	0.94	2000	0.25	0.969
this study	histopathologic sign of infection persistence at SES	62 Knee-Spacers (28 for SWBCC)	0.03	1.00	3250	0.357	0.929
	at least two identical tissue cultures at SES or growth of a virulent microorganism	94 Knee-Spacers (39 for SWBCC)	0.00	0.99	4450	0.50	0.865

SFC: synovial fluid culture; SWBCC: synovial white blood cell count; SES: second stage; PJI: periprosthetic joint infection; MSIS: Musculoskeletal Infection Society.

for $SFC_{(histo)}$. Additionally, 91.7% of the culture positive PJIs at stage one were pathogen eradicated at stage two, but from histopathology negative PJI at initial diagnosis 68.4% were assessed with persistent infection at planned reimplantation. Histopathological studies indicate that neutrophil counts are substantially higher in case of infection persistence at stage two compared to initial PJI diagnosis [23]. This issue was recently highlighted by George et al. who demonstrated low sensitivity of frozen section for ruling out septic failure after reimplantation [24]. Thus, the criteria for histopathological analysis at planned reimplantation for evaluation of infection persistence clearly need clarification and validation.

Follow-up studies could confirm the low sensitivity of IA on the bases of reinfection, instead of clinical, microbiological, and histopathological findings at planned reimplantation. Zmistowski et al. defined infection persistence amongst other features by the need for septic revision due to same causative organism and reported a sensitivity of only 44% for the SWBCC [16]. However, under consideration of the statistic frequencies of causative organisms this approach is also limited by the inability to discriminate infection recurrence to new infection. It is agreed that pathogen detection and histopathologic evaluation are major columns with high sensitivities and specificities for PJI diagnosis [7, 17, 25, 26]. With our approach we must conclude that the value of IA for the question what to expect from sampling at planned reimplantation is insignificant. This conclusion is emphasized by the low sensitivities that have been recently reported for the hip or combined for the hip and the knee, irrespectively of the definition of infection persistence (Table 4) [12, 14, 20, 27]. The current study confirms these low sensitivities particularly at the knee.

Although we had comparable high numbers for microbiologic evaluation, a further limitation to this study is the few cases of infection persistence. But still, this study demonstrates that the $SCF_{(culture)}$ failed to identify these patients. Owed to the fact that before this study we preferred performing the SFC over the SWBCC, the numbers for evaluating the optimal cut-off for the SWBCC are low. Thus, only if enough synovia was aspirated, SWBCC could be analyzed. For the $SWBCC_{(culture)}$, the calculations are based on only two cases with culture positive infection persistence. Thus, our highest Youden-Index is rather low, and compared to the data derived from either hips or hips and knees, our calculated thresholds for SWBCC are high. The variation of thresholds and sensitivities may be attributed to statistical methods, different rates of infection persistence, and infection persistence definitions (Table 4). Although the thresholds for synovial leukocyte count proposed for PJI diagnosis by the Musculoskeletal Infection Society and by the European Bone and Joint Infections Society are well established, they should not replace the lack of a consented cut-off value at IA [11, 17, 28]. In case that SWBCC is preformed, the result needs to be interpreted with respect to clinical parameters and the patients' overall health condition. Low thresholds lead to low specificities and thus bear the risk of overtreatment with inadequate spacer exchange and another course of antibiotic administration. High levels can confirm infection persistence but are rare.

While the SFC adds no information to the question of infection persistence during the TSE, the SWBCC may help to confirm infection persistence in selected cases.

5. Conclusion

The detection of infection persistence remains challenging and a consented approach is lacking. The results do not warrant the routine performance of SFC during the two-stage exchange at the knee. SWBCC can be used to confirm infection persistence at high cut-offs, but they only occur in few patients and are therefore inappropriate for the routine use.

Data Availability

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

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Histopathology in Periprosthetic Joint Infection: When Will the Morphomolecular Diagnosis Be a Reality?

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The presence of a polymorphonuclear neutrophil infiltrate in periprosthetic tissues has been shown to correlate closely with the diagnosis of septic implant failure. The histological criterion considered by the Musculoskeletal Infection Society to be diagnostic of periprosthetic joint infection is "greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification." Surgeons and pathologists should be aware of the qualifications introduced by different authors during the last years in the histological techniques, samples for histological study, cutoffs used for the diagnosis of infection, and types of patients studied. Recently, immunohistochemistry and histochemistry studies have appeared which suggest that the cutoff point of five polymorphonuclear neutrophils in five high-power fields is too high for the diagnosis of many periprosthetic joint infections. Therefore, morphomolecular techniques could help in the future to achieve a more reliable histological diagnosis of periprosthetic joint infection.

1. Introduction

Periprosthetic joint infection (PJI) is one of the most common complications in hip, knee, shoulder, and ankle replacements. For many years, there were no universally accepted criteria for the definitive diagnosis of PJI; each author or scientific society used their own gold standard, which might include clinical, analytical, radiological, microbiological, or histological features. Some authors considered only cultures [1], while others combined histology and cultures [2], and still others added analytical tests [3]. Despite these differences, the histological study of periprosthetic tissue has always been a major component of the attempts to confirm or rule out PJI, and its importance is reflected by its inclusion among the new criteria for PJI infection described by the Musculoskeletal Infection Society (MSIS) in 2011 [4]. Today these criteria have been adopted universally by physicians and surveillance authorities (including the centers for disease control, medical and surgical journals, and the medicolegal community) and by all those involved in the management of PJI [5].

The presence of a polymorphonuclear neutrophil (PMN) infiltrate in periprosthetic tissues has been shown to correlate closely with the diagnosis of septic implant failure. However, the extent of the PMN infiltrate that is required to establish a diagnosis of infection is controversial [6]. The histological criterion considered by the MSIS to be diagnostic of PJI is "greater than five neutrophils per high-power field in five high-power fields observed from histologic analysis of periprosthetic tissue at ×400 magnification" [4]. To many, this definition appears to be oversimplified. The utility of histological diagnosis, in terms of its sensitivity, specificity, and positive and negative predictive values, may vary depending on the technique used, the sample studied, the cutoff point used to define PMN infiltration, and patient- associated factors.

The aim of the present review is to examine the origin of the MSIS' current definition of histological PJI and to consider what morphomolecular studies can add to the histological diagnosis of PJI.

2. Histological Techniques

In PJI, two histological techniques have been used: frozen sections for intraoperative histological assessment and paraffin sections for final or postoperative assessment [7]. Classically, both techniques use hematoxylin-eosin staining; both provide information on the likelihood of infection, but their aims are qualitatively different [7]. Intraoperative histology aims to inform the surgeon during the operation whether the prosthesis to be replaced is infected or not. This helps the surgeon to decide whether to implant the definitive prosthesis in an area that is probably infected (a one-stage revision) or to insert a cement spacer with antibiotics before implanting the definitive prosthesis several weeks or months later (a two-stage revision).

The major objective of the definitive postoperative histology is to establish whether the prosthesis was infected. In this regard, it serves as a confirmatory test for infection a posteriori once the new prosthesis has been implanted. Postoperative histology is also useful in diagnosing those cases of PJI which were thought preoperatively, on the basis of clinical and laboratory findings, to be aseptic in nature.

As a result, intraoperative histology is used to guide surgical decisions (i.e., whether or not to implant the definitive prosthesis), and definitive histology, in conjunction with other data such as microbiological results [3], is used to make medical decisions (e.g., whether to administer antibiotics). Another important difference is that although the frozen section diagnosis of septic loosening is based on similar criteria, the morphological identification of neutrophils and their differentiation from other inflammatory elements within periprosthetic tissues is more difficult in frozen sections than in paraffin sections [15]. Some authors report few differences between the results of frozen and paraffin sections, but others have found major discrepancies. Stroh et al. [38] reported a concordance of 97.7% in 304 frozen and permanent sections and the difference did not affect the final outcome of the patients. However, Tohtz et al. [37] reported a 21.8% discrepancy (14 of 64 cases) comparing frozen and paraffin sections. In 12 patients (18.8%), the diagnosis of the frozen sections was ambiguous or unclear, and permanent sections confirmed the diagnosis (the final diagnosis was aseptic loosening in eight patients and septic loosening in four) as the tissue samples were not sufficiently representative for cryohistology. In two patients (3.2%), the diagnosis of the intraoperative frozen section was aseptic loosening and the diagnosis of the permanent sections was septic. Therefore, whenever we evaluate histological results we must be clear whether we are dealing with frozen or paraffin sections, as paraffin section histology avoids or reduces histological technical bias [15].

3. Samples for Histological Study

During the revision arthroplasty the surgeon can obtain various samples of periprosthetic tissue for histological analysis. The tissues available are samples of synovium/pseudocapsule, the periprosthetic membrane, and other periprosthetic tissues in which infection is suspected. The literature review (Table 1) shows that the specimens submitted for histological evaluation present considerable variability, and this variability may affect the pathology results. Nevertheless, most authors agree that the best sample for histological study of PJI is the periprosthetic membrane. One study [45] that compared the interface membrane and the pseudocapsule concluded that the interface membrane had a higher sensitivity and predictive values for identifying neutrophils. Specifically, this study found that the proportion of infected patients with positive interface membrane was significantly higher than that among those with positive pseudocapsule (83% versus 42%, $P = 0.04$). A possible reason for these results could be the presence of fibrosis in the pseudocapsule which hindered neutrophil infiltration or that the largest bacterial biofilm is found between implant and bone. In addition, one group [46] recently used membranes (not the pseudocapsule) and have proposed a histopathological consensus classification for a standardized evaluation of periprosthetic tissues. Both these studies [45, 46] support the use of the interface membrane as a reference tissue for histological study.

4. Cutoffs Used for the Diagnosis of Infection

The histological criterion used to diagnose whether a prosthesis is infected or not is the presence or absence of PMNs (Table 1). Some authors have also assessed the presence of other cells such as lymphocytes or plasma cells [11, 15, 28]. PMNs are found in infected tissue, but their presence in uninfected tissue is minimal or absent. The results in Table 2 vary because the authors used different gold standards and different patient groups for comparison of the histology tests. The first of these discrepancies may possibly be solved in the future with the introduction of the new definition proposed by the MSIS for periprosthetic infection. The second is more difficult to resolve because it depends on whether all consecutively operated patients are studied or only the ones with a high suspicion of infection [7]. Analysing the histology results from all patients undergoing revision arthroplasty is likely to yield lower specificity and positive predictive values than the results obtained if only patients with a clinical suspicion of infection at the time of surgery are assessed [7].

As with all diagnostic tests, if we raise the histology test's cutoff point for defining infection to ten PMNs, we reduce the sensitivity while increasing the specificity; if we lower it to one PMN, the reverse is the case. The new definition proposed by the MSIS for periprosthetic infection uses five PMNs as cutoff point, because it is the most frequently used worldwide and because several studies have shown that there is no difference between using five or ten PMNs [6, 17, 22]. However, certain microorganisms, especially coagulase-negative staphylococci (CNS) and *P. acnes*, can cause a periprosthetic infection with a PMN infiltration rate below five [11, 23, 35, 42, 47].

5. Types of Patients Studied

The type of patient studied may also introduce a major bias in the definition of the sensitivity, specificity, and positive and negative predictive values of histology tests. This is due to the difference in incidence of low-grade infection (CNS and *P. acnes*) or virulent infection. Most authors

Table 1: Summary of the main articles with the type of specimens used for the histological study and the histological criteria for interpretation of histology as diagnostic of infection.

Reference	Specimen	Criteria
Mirra et al. (1976) [8]	Synovial and capsular tissues	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (500x)
Fehring and McAlister (1994) [9]	Joint pseudocapsule, interface membrane, and any area that appeared suspicious for possible infection	Evidence of acute inflammation (no quantification)
Feldman et al. (1995) [10]	Joint pseudocapsule and interface membrane	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Athanasou et al. (1995) [11]	Joint pseudocapsule and interface membrane	≥1 polymorphonuclear leukocyte per HPF on average in at least 10 HPF (400x)*
Lonner et al. (1996) [12]	Joint pseudocapsule, interface membrane, and any area that appeared suspicious for possible infection	≥5 and ≥10 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Pace et al. (1997) [13]	Joint pseudocapsule and interface membrane	≥5 polymorphonuclear leukocytes per HPF on multiple (three) HPF (600x)
Abdul-Karim et al. (1998) [14]	Interface membrane (aseptic suspicion). Interface membrane, synovial tissue, and unusually discolored tissue (septic suspicion)	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Spangehl et al. (1999) [3]	Synovial surface	≥5 polymorphonuclear leukocytes in any single HPF (400x)
Pandey et al. (1999) [15]	Joint pseudocapsule and interface membrane	≥1 polymorphonuclear leukocyte per HPF on average in at least 10 HPF (400x)*
Pons et al. (1999) [2]	Synovial surface	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Della Valle et al. (1999) [16]	Joint pseudocapsule, granulation tissue, and any area that appeared suspicious for possible infection	-
Banit et al. (2002) [17]	Joint pseudocapsule and any area that appeared suspicious for possible infection	≥10 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Musso et al. (2003) [18]	Joint pseudocapsule, interface membrane, and any area that appeared suspicious for possible infection	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Malhorta and Morgan (2004) [19]	Joint pseudocapsule	≥5 polymorphonuclear leukocytes per HPF in most areas (400x)
Ko et al. (2005) [20]	Joint pseudocapsule, interface membrane, and any area that appeared suspicious for possible infection	≥5 polymorphonuclear leukocytes in any single HPF (400x)
Wong et al. (2005) [21]	Synovial surface, joint pseudocapsule, and interface membrane	≥5 and ≥10 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Francés Borrego et al. (2006) [22]	Periprosthetic soft tissue	≥10 polymorphonuclear leukocytes in any single HPF (400x)
Bori et al. (2006) [23]	Joint pseudocapsule, interface membrane, and any area that appeared suspicious for possible infection	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Morawietz et al. (2006) [24]	Interface membrane	Evidence of acute inflammation (no quantification). Low or high grade.
Nuñez et al. (2007) [25]	Joint pseudocapsule, interface membrane, and any area that appeared suspicious for possible infection	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Nilsdotter-Augustinsson et al. (2007) [26]	Synovial surface and interface membrane	≥5 polymorphonuclear leukocytes in any single HPF (400x)
Della Valle et al. (2007) [27]	Synovial surface	≥10 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Bori et al. (2007) [28]	Joint pseudocapsule, interface membrane, and any area that appeared suspicious for possible infection	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)

Table 1: Continued.

Reference	Specimen	Criteria
Kanner et al. (2008) [29]	Periprosthetic soft tissue	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Müller et al. (2008) [30]	Interface membrane	Evidence of acute inflammation (no quantification)
Schinsky et al. (2008) [31]	Synovial surface	≥10 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Fink et al. (2008) [32]	Periprosthetic tissue	≥5 polymorphonuclear leukocytes in any single HPF (400x)
Schäfer et al. (2008) [33]	Periprosthetic soft tissue and membrane	≥5 polymorphonuclear leukocytes per HPF in ≥10 HPF (400x)
Savarino et al. (2009) [34]	-	≥1 polymorphonuclear leukocytes in any single HPF (600x)
Bori et al. (2009) [35]	Joint pseudocapsule, interface membrane, and any area that appeared suspicious for possible infection	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Morawietz et al. (2009) [36]	Interface membrane	≥23 polymorphonuclear leukocytes in ≥10 HPF (400x)**
Tohtz et al. (2010) [37]	Interface membrane	≥2 polymorphonuclear leukocytes per HPF in at least 10 HPF (400x)
Stroh et al. (2012) [38]	Joint pseudocapsule, synovium, and soft tissue	Mean of greater than 5 polymorphonucleocytes (PMNs) per HPF was the criteria
Miyamae et al. (2013) [39]	Periprosthetic tissue	≥10 polymorphonuclear leukocytes in any single HPF (400x)
Ahmadi et al. (2013) [40]	Periprosthetic tissue	≥5 polymorphonuclear leukocytes in any single HPF (400x)
Muñoz-Mahamud et al. (2013) [41]	Interface membrane	≥5 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Grosso et al. (2014) [42]	Joint pseudocapsule and interface membrane	≥10 polymorphonuclear leukocytes per HPF in ≥5 HPF (400x)
Buttaro et al. (2015) [43]	Joint pseudocapsule, interface membrane, and any other tissue involved according to the surgeon's judgment	≥5 polymorphonuclear leukocytes per HPF in at least 10 HPF (400x)
Kashima et al. (2015) [44]	Joint pseudocapsule and interface membrane	≥2 polymorphonuclear leukocytes per HPF on average in at least 10 HPF (400x)***

*≥1 polymorphonuclear leukocyte per HPF on average after examination of at least 10 HPF; **≥23 polymorphonuclear leukocytes in ≥10 HPF (400x). In each HPF, a maximum of 10 polymorphonuclear leukocytes were counted. The sum must be between zero and 100; ***≥2 polymorphonuclear leukocytes per HPF on average after examination of at least 10 HPF.

have tried to assess the true value of this test using the postoperative diagnosis, that is, after the definitive diagnosis of the replacement as septic or aseptic has been established. However, one author assessed the value of the histology test based on the preoperative diagnosis, the suspicion of loosening (either septic or aseptic), or whether it was the time of reimplantation of a definitive prosthesis [23, 28, 35]. This is an interesting strategy, since the distribution of microorganisms responsible for the infection differs in each group [47–49] and this may be the cause of the discrepancies in the test results. When we find patients with a preoperative suspicion of aseptic loosening, only a small number (about 10%) of those with positive cultures are definitely infected, with the microorganisms most commonly responsible for this infection being CNS [23, 47, 48]. Therefore, as Bori et al. [23] reported, histology has low sensitivity in these patients. In a study of 61 replacements with a preoperative suspicion of aseptic loosening, the cultures were positive in 12 cases and CNS were the most common microorganisms (11 cases). Only in six out of 12 cases (50%) did the histology reveal more than five polymorphonuclear leukocytes per high-power field. There is a danger that the high negative predictive value of histology in cases with low suspicion of infection might be used to exclude infection incorrectly.

In patients with a preoperative suspicion of septic loosening, the microorganisms responsible presented a classic distribution of chronic infection with the presence of CNS, *S. aureus*, Gram-negative bacilli, and others; therefore, as many authors have reported [49–51], the histology test is likely to have a high sensitivity since CNS are not the microorganisms with the highest global prevalence. In a study [35] of 38 replacements with a preoperative suspicion of septic loosening (in which CNS were the etiology in 13 cases, Gram-negative bacilli in eight, *Staphylococcus aureus* in seven,

Table 2: Sensitivity, specificity, and positive and negative predictive values.

	N	Cutoff PMN	*S* (%)	*E* (%)	PPV (%)	NPV (%)
Mirra et al. (1976) [8]	34	5	100	98	-	-
Fehring and McAlister (1994) [9]	107	Total	18	89	-	-
Feldman et al. (1995) [10]	33	5	100	96	-	-
Athanasou et al. (1995) [11]	106	1	90	96	88	98
Lonner et al. (1996) [12]	175	5	84	96	70	98
Lonner et al. (1996) [12]	175	10	84	99	89	98
Pace et al. (1997) [13]	25	5	82	93	90	87
Abdul-Karim et al. (1998) [14]	64	5	43	97	-	-
Spangehl et al. (1999) [3]	202	5	80	94	74	96
Pons et al. (1999) [2]	83	5	100	98	94	100
Della Valle et al. (1999) [16]	64*	5	25	98	50	95
Banit et al. (2002) [17]	121	10 (knee and hip)	67	93	67	93
Banit et al. (2002) [17]	55	10 (knee)	100	96	82	100
Banit et al. (2002) [17]	63	10 (hip)	45	92	55	88
Musso et al. (2003) [18]	45	5	50	95	60	92
Ko et al. (2005) [20]	40	5	67	97	86	91
Wong et al. (2005) [21]	40	5	93	77	68	95
Wong et al. (2005) [21]	40	10	86	85	75	92
Francés Borrego et al. (2006) [22]	63	10 (knee)	66	89	81	81
Francés Borrego et al. (2006) [22]	83	10 (hip)	50	100	100	95
Bori et al. (2006) [23]	61	5	50	81	40	86
Nuñez et al. (2007) [25]	136	5	85	87	79	91
Nilsdotter-Augustinsson et al. (2007) [26]	85	5	81	100	100	87
Della Valle et al. (2007) [27]	105	10 (knee)	88	96	91	93
Bori et al. (2007) [28]	21	5	28	100	100	73
Bori et al. (2007) [28]	21	1	71	64	50	81
Kanner et al. (2008) [29]	132	5	29	95	40	92
Müller et al. (2008) [30]	37	Total	94	94	97	86
Schinsky et al. (2008) [31]	201	10 (hip)	73	94	82	90
Fink et al. (2008) [32]	145	5	90	95	88	96
Savarino et al. (2009) [34]	31	1	80	100	100	80
Morawietz et al. (2009) [36]	147	23*	73	95	91	84
Tohtz et al. (2010) [37]	52	23*	86	100	100	94
Miyamae et al. (2013) [39]	86	10	71	89	42	97
Ahmadi et al. (2013) [40]	227	5 (elbow)	51	93	60	90
Muñoz-Mahamud et al. (2013) [41]	11	5 (fracture)	100	55	33	100
Grosso et al. (2014) [42]	44	5 (shoulder)	57	100	-	-
Grosso et al. (2014) [42]	44	10 (shoulder)	73	100	-	-
Buttaro et al. (2015) [43]	76	5	90	94	87	96
Kashima et al. (2015) [44]	76	2	94	97	-	-
Kashima et al. (2015) [44]	76	5	83	97	-	-

N: number of patients, PMN: polymorphonuclear neutrophil, *S*: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value; * ≥23 polymorphonuclear leukocytes in ≥10 HPF (400x). In each HPF, a maximum of 10 polymorphonuclear leukocytes were counted. The sum must be between zero and 100.

Candida sp. in two, *Peptococcus* sp. in two, *Enterococcus* sp. in one, and *S. pneumoniae* in one, and no clearly identifiable microorganism was responsible in four), the histology tests were positive in all except two of the 13 caused by CNS.

One interesting group is those recently operated patients who have a cement spacer and require the placement of the definitive prosthesis. As in the first group, positive cultures in these patients are very likely to be due to a CNS or *P. acnes*. The only two specific studies [16, 28] of this group of patients in the literature both conclude that histology has a low sensitivity. In a study [28] with 21 patients at the time of reimplantation, in which seven had positive cultures (six due to CNS and one to *Candida* sp.), the histology was positive in only two cases (one case caused by CNS and the other

by *Candida* sp.). The other study [16] reported that only four patients out of 64 were considered to have a persistent infection on the basis of positive intraoperative cultures or permanent histological sections. Overall, intraoperative analysis of frozen sections at the time of reimplantation after resection arthroplasty had a sensitivity of 25%; only one out of four persistent infections was detected. The study did not describe the organisms responsible for the infection.

Most of these studies were performed with revision arthroplasties of the knee and hip, but recently studies of revision arthroplasties of the shoulder [42] and elbow [40] have shown that histology has low sensitivity. This is due not to the type of prosthesis or joint, but to the fact that most infections in shoulder prostheses are due to *P. acnes* and most infections in elbow prostheses are due to CNS *and P. acnes*. In a study [42] of 45 patients with replacements of a shoulder prosthesis, of whom 30 presented infection, *P. acnes* was the etiology in 18 cases and other microorganisms in 12. The sensitivity was lower for the *P. acnes* group (50%) than for the other infections group (67%).

Finally, there are two groups of patients in which histology produces a high rate of false positives for diagnosis of infection: patients who undergo a prosthetic replacement and have an underlying inflammatory disease (e.g., rheumatoid arthritis) [52] and those receiving a prosthetic replacement for a periprosthetic fracture [11, 41]. The first group of patients have a persistent neutrophil infiltration in the periprosthetic tissues due to the underlying active disease and not due to prosthetic infection. Kataoka et al. [52] studied synovial tissue in 60 joints from rheumatoid arthritis patients at the time of the placement of an arthroplasty and found 10 cases with more than five PMNs per high-power field. They concluded that PMNs in the rheumatoid synovium were a common microscopic finding and that the presence of more than five PMNs per high-power field in the rheumatoid synovium was not necessarily consistent with infection. The second group of patients had an acute neutrophil infiltration in periprosthetic tissues due to the fracture. In a study [41] of 11 patients undergoing replacement due to periprosthetic fracture, Muñoz-Mahamud et al. [41] found only two patients with positive cultures, but histology was positive for infection in six cases; that is, the false positive rate was 66.6%. A possible explanation for these results might be the infiltration of neutrophils into the periprosthetic membrane, proceeding from the inflammation secondary to the fracture and from the blood vessels injured during the fracture. Another group in which PMNs can be identified in periprosthetic tissues with increased frequency is that of failed metal-on-metal hip replacements, although numbers greater than five PMNs per high-power field are seen only in microbiologically confirmed cases of PJI [53].

6. Is the Morphomolecular Diagnosis the Future?

As we have seen, all the studies analysed to determine the presence of PJI have used hematoxylin-eosin histological staining and have assessed the presence of a neutrophil polymorph infiltrate in periprosthetic tissues. Sometimes it is difficult to identify neutrophils, even using Feldman et al.'s criteria [10]. The Feldman et al.'s criteria are as follows: First, the tissue had to be pink-tan and not simply white scan, to avoid analysis of dense fibrous tissue or fibrin. Second, at least two specific tissue samples were used in order to minimize the risk of sampling error. Third, the five most cellular areas in the tissue sample were chosen for evaluation. Fourth, all polymorphonuclear leukocytes had to have defined cytoplasmic borders to be included. Debris that appeared to be the result of nuclear fragmentation was excluded, as it could not be categorized definitively as a polymorphonuclear leukocyte. Fifth, five separate fields were evaluated under high-power magnification (forty times) and the histology was considered positive for infection if there were more than five polymorphonuclear leukocytes per high-power field in at least five separate microscopic fields. A possible strategy to favor the development of a histological morphomolecular diagnosis would be to stain or identify the presence or absence of PMNs, using the molecular markers that they contain. Two authors [36, 44] have applied this approach in recent clinical studies, though using different strategies. In 2009, Morawietz et al. [36] used immunohistochemistry (CD15), and in 2015, Kashima et al. used histochemistry alone [44]. Morawietz et al. [36] reached the conclusion that 23 PMNs in 10 HPF (visual field diameter 0.625 mm) was the cutoff point to differentiate infected from noninfected tissues (with tissues containing more than 23 PMNs being infected). In this study the authors used CD15 immunohistochemistry to identify PMNs, as follows: The antigen was retrieved with Tris buffer (Target Retrieval Solution High pH; DAKO Cytomation, Glostrup, Denmark) in a pressure cooker for 5 min. Endogenous peroxidase was blocked with 3% peroxide for 10 min. The primary antibody (monoclonal mouse antihuman CD15, clone C3D-1; Dako) was incubated for 30 min at a 1 : 50 dilution. The antibody was visualized with the Labelled Streptavidin–Biotin+ system (Dako) following the manufacturer's instructions. In this way, in contrast to previous clinical studies, identification of PMN was not based on cell morphology alone, but on immunohistochemistry as well. Ideally, PMNs can be identified by their small, lobulated nuclei and their narrow cytoplasmic rim. However, the prosthetic wear-particles or bone fragments, which occur frequently in periprosthetic membranes, make precise microsectioning of these tissues difficult and may lead to artefacts or rather thick sections, complicating the precise identification of PMN. Quantification was therefore performed using CD15 immunohistochemistry for the identification of PMN. The authors [36] concluded that immunostaining obtains more accurate counting of PMN than hematoxylin and eosin staining and PAS staining analysed also in the same study.

Kashima et al. [44] reported that the histological criterion of more than two PMNs per HPF showed increased sensitivity and accuracy for the diagnosis of septic loosening. In that study [44] the authors used chloroacetate esterase (CAE) enzyme histochemistry to identify PMNs, applying the following histological technique: Briefly, Naphthol AS-D chloroacetate (5 mg, SIGMA, St. Louis, MO) in

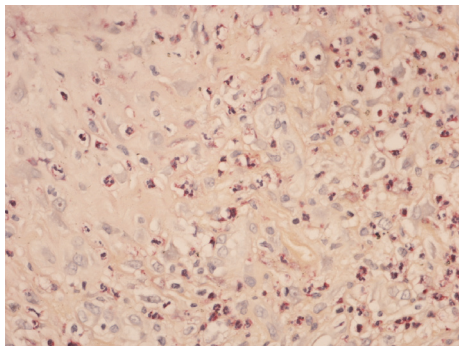

Figure 1: Heavily inflamed granulation tissue in which there are numerous neutrophil polymorphs (>5 per high-power fields) with chloroacetate esterase staining.

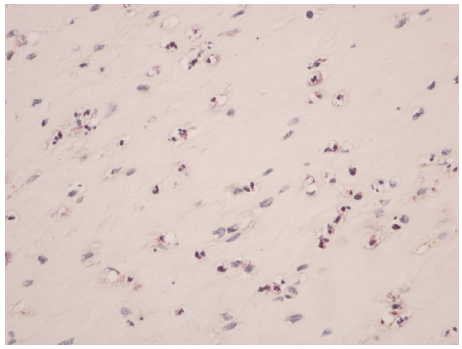

Figure 2: Frozen section of inflammatory tissue showing chloroacetate esterase staining + neutrophil polymorphs (>5 per high-power fields).

N,N-dimethylformamide was gently mixed with Fast Red GBP Salt (SIGMA) in 0.2 M phosphate buffer, pH 6.4 (5 mg/50 mL). The solution was filtered and applied to sections in a 50 mL Coplinger for 5 min for frozen sections and for 45 min for formalin-fixed paraffin-embedded sections. Sections were counterstained with Mayer's hematoxylin. CAE enzyme histochemistry has been used for many years in hematopathology to detect granulocytes and to distinguish them from other myeloid series cells. In their study, Kashima et al. [44] established that CAE staining facilitates the identification of PMN in frozen and paraffin sections of periprosthetic tissues in cases of septic loosening of hip and knee arthroplasties, and they also reassessed the number of PMNs correlating with septic or aseptic hip and knee implant failure (Figures 1, 2, and 3).

Morawietz et al. [36] and Kashima et al. [44] came to similar conclusions: 23 PMNs in 10 HPF or two PMN in one HPF are indicative of PJI. Their observations suggest that the histological criterion of more than five neutrophils per HPF, considered diagnostic of infection by the MSIS, is too high [54]. A small difference between these two authors is that they use different methods to count the PMNs identified. Morawietz et al. [36] counted all the immunoreactive (red) cells on the CD15-stained slides, regardless of their morphology. In each HPF, a maximum of 10 PMNs was counted. If more PMNs were present in one HPF, the count was limited

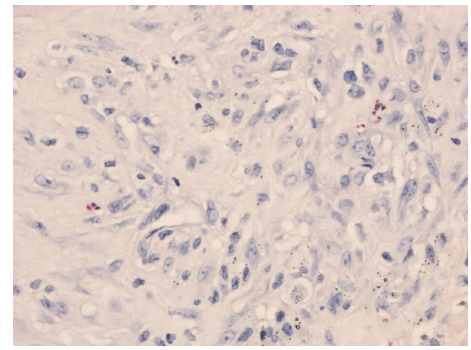

Figure 3: An area of capsular tissue showing chloroacetate esterase staining in which there are fewer than 5 neutrophil polymorphs per high-power field.

to 10 PMNs. Ten HPF were examined in this way, so the maximum count per case was 100 PMNs. Kashima et al. [44] examined at least five (×400) HPF (1.55 mm^2) in five different areas of each histological section (i.e., 25 HPF) and counted the number of PMNs in these five areas. From this, the average number of PMN per HPF was calculated and the polymorph infiltration score determined as follows: 0 means no polymorphs identified, + means fewer than two polymorphs per HPF (×400), ++ means two to five cells per HPF, and +++ means more than five cells per HPF. The ways used to count the PMNs do not seem to affect the conclusions reached by the two authors. Their results corroborate those of previous studies which stated or inferred that infections due to CNS or *P. acnes* might have a PMN infiltration of fewer than five per HPF.

Another strategy for developing the histological morphomolecular diagnosis in PJI is first to define the molecules that are present in infected periprosthetic tissues and absent in uninfected tissues. Recently, two studies [55, 56] have sought to define biomarkers in the synovial fluid in order to identify PJI, but few have defined biomarkers in solid periprosthetic tissues. Testing 16 biomarkers by immunoassay in synovial fluid, Deirmengian et al. [55] found that five biomarkers, namely, human alpha-defensin 1–3, neutrophil elastase 2, bactericidal/permeability-increasing protein, neutrophil gelatinase-associated lipocalin, and lactoferrin, correctly predicted the MSIS classification of all patients, with 100% sensitivity and specificity for the diagnosis of PJI. Therefore, synovial fluid biomarkers may be a valuable addition to the methods used for the diagnosis of PJI in the future. These biomarkers are all host proteins with direct antimicrobial activity, playing important roles in the innate response for eliminating pathogens. When pathogens are present, these biomarkers become more concentrated in the synovial fluid. The problem is that the biomarkers have not been studied in the tissues where they are produced, only in the synovial fluid. Identifying a local host response to bacteria within the periprosthetic tissues would theoretically provide a sensitive and specific test for PJI without the potential for contamination or failure to culture the infecting organism.

CD15 has been the most important tissue biomarker used in clinical and experimental histological studies to distinguish between septic and aseptic loosening [36, 57]. Tamaki et al. [57] reported that aseptic periprosthetic tissue contained numerous CD68-positive monocytes/macrophages in focal stromal cellular infiltrates and in synovial lining. The tissues were also characterized by well-organized and often dense fibrous connective tissues. PMNs were observed only rarely, although a few scattered CD15+ cells were seen in the synovial lining and sublining layers and in perivascular areas. In septic periprosthetic tissues, stromal fibroblasts and marked cellular infiltration with mononuclear cells were observed, associated with fibrous loose connective tissues and a few neovessels. The infiltrating cells were mostly PMNs, which were stained with CD15. The most important problem is that CD15 is not specific for PMN.

Toll-like receptors (TLR) are other tissue biomarkers that have been studied histopathologically in PJI. Takagi et al. [58] and Lähdeoja et al. [59] reported their presence in loosening. Lähdeoja et al. [59] found that the aseptic synovial membrane (aseptic revision) contained markedly more TLR-positive cells per high-power field than osteoarthritic synovium. TLR proteins 1–9 were stained manually using affinity-purified rabbit anti-human IgG antibodies specific for TLR 1 (0.80 mg/mL), TLR 2 (2.7 mg/mL), TLR 3 (2 mg/mL), TLR 4 (1.3 mg/mL), TLR 5 (0,8 mg/mL), TLR 6 (1 mg/mL), TLR 7 (0.8 mg/mL), TLR 8 (2.7 mg/mL), or TLR 9 (0.5 mg/mL), all from Santa Cruz Biotechnology (Santa Cruz, CA). Therefore it seems that prosthetic loosening enhances expression of inflammatory markers that may be useful for morphomolecular diagnosis.

Subsequent studies have tried to identify the specific TLR associated with infection and sought to distinguish between infected and noninfected tissues histologically. Tamaki et al. [57] reported that samples from aseptic loosening, septic loosening, and osteoarthritic synovium showed immunoreactivity for TLR 2, 4, 5, and 9. Monocyte/macrophage infiltrates with marked immunoreactivity of TLR 2, 4, 5, and 9 were observed in the synovial lining in both the interface and regenerated capsular tissues retrieved from aseptically loosened hip joints. In the septic tissues, immunoreactivity to TLR 2, 4, 5, and 9 was detectable in PMN cell infiltrates and in the few monocyte/macrophage-like cells that were also present. In contrast, in osteoarthritis only modest reactivity to TLR 2, 4, 5, and 9 was seen in the endothelial cells and synovial lining. Deirmengian et al. [55] concluded that an increase in expression of TLR can be found in the synovial-like interfacial membrane in aseptic periprosthetic and septic synovial cases compared to osteoarthritic tissues. These TLR cannot be used to differentiate between aseptic and septic tissue in terms of their quantity; however, if we consider their cell location, TLR 2, 4, 5, and 9 were found in monocyte/macrophages in aseptic replacements and in PMNs in septic replacements. Recently, Cipriano et al. [60] in 2014 demonstrated significant increases in the expression of TLR 1 and 6 in infected compared with noninfected tissue obtained during revision total knee or hip arthroplasty. However, TLR1 expression was more accurate in predicting PJI than TLR6 or TLR10. The drawback of this study is that it was not a histological study; the authors used a real-time PCR in homogenized tissue specimens. Therefore, a histological study with TLR1 is required to confirm these results.

7. Conclusion

Despite the large number of studies in this field over the past 40 years, the current histological criterion for PJI stipulated by the MSIS (more than five PMNs in five HPF) remains the one proposed by Mirra et al. [8] in 1976. Surgeons and pathologists should be aware of the qualifications introduced by different authors since then, for instance, the fact that infections due to CNS may have an infiltration of fewer than five PMN or that periprosthetic fractures may give false positive results on histological diagnosis. The histological diagnosis is very important in the assessment of PJI, but many hospitals ignore it. Often there may be no pathologist available to make the diagnosis, or communication between the surgeon and the pathologists is poor. Also, surgeons may not be familiar with the histological techniques (HPF, etc.) or do not know the significance of diagnosis established with frozen section or paraffin section histology. In recent years, immunohistochemistry and histochemistry studies have appeared which suggest that the cutoff point of five PMNs in five HPF is too high for the diagnosis of many PJI. Rather than H-E staining (the classical nonspecific staining), these studies use more specific staining for PMN, such as CD15 and CAE. These developments suggest that we should identify the most cost-effective techniques to mark PMN as specifically as possible, so as to be able to identify and count them and make an accurate diagnosis of PJI. Morphomolecular techniques could help to achieve a more reliable histological diagnosis of PJI.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Different Kinetics of Perioperative CRP after Hip Arthroplasty for Elderly Femoral Neck Fracture with Elevated Preoperative CRP

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This study aimed to determine the kinetics of four inflammatory markers and to identify the variables that affect the natural kinetics of inflammatory markers in aged patients having hip fractures with and without elevated preoperative CRP. 240 elderly patients who have been operated on for femoral neck fracture with no infectious complications were divided into two groups on elevated preoperative CRP level (>10 mg/L). The temporal values of four inflammatory markers of WBC, neutrophil count (*N*) (%), ESR, and CRP were assessed eight times every other day until the 14th postoperative day. At 48–60 h postoperatively, mean CRP was markedly higher in patients with preoperatively elevated CRP than in those with nonelevated CRP (122.1 ± 65.9 and 73.7 ± 35.5, $p < 0.001$). However, the abrupt elevation of CRP in the elevated group was conversely decreased on the 4th-5th postoperative day, demonstrating similar kinetic curves with no significant differences between both groups. For WBC, *N* (%), and ESR, both groups showed similar patterns of temporal values 14 days after surgery regardless of preoperative CRP level. Our findings could be used as guidelines for patient discharge and during the follow-up period after surgery.

1. Introduction

Arthroplasty is strongly recommended for elderly patients with unstable (displaced) femoral neck fracture [1]. In a subset of patients, delayed treatment due to several reasons can lead to higher mortality from concomitant medical problems. Several studies have indicated the advantage of surgery within 48 h, supporting that hip fracture surgery within 48 h of admission is associated with better outcomes [1]. However, an elevated level of C-reactive protein (CRP) can be a basis for delaying surgery, and it is one of the criteria for periprosthetic joint infection (PJI) diagnosis after surgery [2].

In elderly patients, femoral neck fractures usually occur following a fall, which can affect general health conditions with pulmonary or urinary infections, resulting in elevated preoperative CRP. In addition, a minimal elevation of CRP in a healthy, aged person might occur secondary to an increase in interleukin-6 gene expression that is related to frailty [3, 4]. Moreover, the level of preoperative CRP can be elevated from fracture itself or elevated in various clinical situations, such as concomitant cardiac disease, without an obvious infection [5].

If the elevated CRP level is caused by factors other than infection, arthroplasty does not need to be delayed simply because of the elevated preoperative CRP level [6]. On the other hand, if the reference level of preoperative CRP is elevated, this can affect the changes in temporal values of inflammatory markers including CRP and erythrocyte

sedimentation rate (ESR) [7]. This may cause confusion during the follow-up period after surgery when determining the need for additional diagnostic procedures to confirm the presence of PJI.

In the postoperative stage, the use of antibiotics decreases the infection rate in total joint arthroplasty [8]; however, it is recommended that the duration of antibiotic prophylaxis should not exceed 24 h postoperatively because of an increased risk of resistance and toxicity [9]. In this sense, understanding the natural kinetics of inflammatory markers after surgery would be helpful for surgeons to determine the duration of antibiotic treatment and can assist in the early detection and monitoring of PJI.

The purpose of this study was to determine whether the perioperative kinetics of four inflammatory markers, white blood cell count (WBC), neutrophil count (*N*) (%), ESR, and CRP, have different patterns in aged patients having hip fractures with and without elevated preoperative CRP, additionally to identify the variables that affect the natural kinetics of inflammatory markers. We hypothesized that preoperative CRP level would affect the changes in temporal values of inflammatory markers after surgery and there would be patients' variables affecting the kinetics.

2. Materials and Methods

This retrospective study included 259 consecutive elderly patients who have been operated on for femoral neck fracture. They were divided into groups of elevated preoperative CRP level (>10 mg/L) and without elevated preoperative CRP level. The medical records of 289 hip hemiarthroplasties (HA) that were performed at our institution from January 2010 to June 2015 were reviewed. The inclusion criteria were as follows: a diagnosis of femoral neck fracture in patients aged above 60, patients admitted until stitches were removed on the 14th postoperative day, and patients followed up for more than 1 year. We excluded patients who had infectious complications of pneumonia (4 patients), PJI or wound infection (5 patients), urinary tract infection (6 patients), and death (4 patients). After these exclusions, 240 patients were identified as eligible for inclusion in this study.

Total patients were divided into two groups, 116 patients with elevated preoperative CRP (elevated CRP group) and 124 patients without elevated preoperative CRP (nonelevated CRP group) (Table 1). All patients or their proxy gave their informed consent to participate in the study, and this study was approved by the Institutional Review Board of our hospital.

A senior surgeon of our group performed all of the surgeries using the posterolateral approach [10]. Patients treated with other approaches or implants and those with pathological fractures were excluded. HA operation was performed in the lateral decubitus position using the posterolateral approach; then capsular repair and repair of the short external rotators were performed with strong nonabsorbable transosseous sutures in the greater trochanter. A Corail™ femoral stem (DePuy J&J, Warsaw, IN) with bipolar head was used in all cases. The incision was closed over a deep suction drain that was removed 48 h later. All patients received the same perioperative management with regard to anesthesia, multimodal analgesics, and wound management. The first wound dressing was placed on the second postoperative day, and wound dressings were routinely changed every other day. All patients were kept on physical (ankle pumps) and chemical prophylaxis for deep vein thrombosis (DVT) during their hospital stay.

The recorded data were reviewed with a focus on demographic characteristics, preexisting comorbidities, type of anesthesia used (general or regional), the duration of Foley insertion, time interval from injury to operation, cemented versus uncemented prosthesis, the number of blood transfusions, and operation time. For a CRP level that was higher than 10 mg/L, HA was performed if there were no clinical signs and symptoms of infectious processes during physical examinations. The clinical signs and symptoms of infectious conditions included fever (>37.3°C), redness, and local heat sensation. Preoperative infection diagnosis and treatment increased the delay before bipolar hemiarthroplasty from 0.7 to 8.3 days. Patients with elevated preoperative CRP were treated with the same protocol as others without elevated preoperative CRP. All patients received the same prophylactic antibiotics (2 g of cefazolin) within 1 h before incision. Intravenous antibiotics were also administered to all patients for 2 days. Allogenic blood transfusion was performed if hemoglobin level fell below 8.0 mg/dL or if anemic symptoms such as dyspnea or tachycardia persisted even after volume replacement in patients with a hemoglobin level between 7.0 and 8.0 mg/dL [11–13]. When transfusion was indicated, one unit of packed red blood cells was transfused at a time to increase the hemoglobin level to 9.0 g/dL. All participants received the recommended thromboprophylaxis regimen (with a low-molecular-weight heparin) from the operative day during 14 days after the operation. Tolerable weight-bearing ambulation was allowed on the second postoperative day after drainage removal.

We routinely evaluated preoperative WBC, *N* (%), CRP, and ESR on the day before surgery. Venous blood samples of all patients were obtained and checked eight times every other day until removal of staples on the 14th postoperative day. During the follow-up period, PJI was diagnosed using the criteria that were previously reported [14] and excluded from the enrolled database.

The current study obtained Institutional Review Board approval from our institution (KANGDONG 2016-11-006) before study onset, and our protocol was also approved. Informed consent was obtained from all participants.

2.1. Statistical Analysis. The temporal values of the four inflammatory markers were compared between the two groups. The values were represented as the mean and standard deviation at each time point. In addition, the changes in patterns of the markers were compared between the elevated and nonelevated CRP groups. The statistical significance of the differences between the two groups at each time point was determined using *t*-test. An a priori power analysis was performed to determine the sample size using the two-sided

Table 1: Patient demographics and baseline characteristics.

	Elevated CRP group (CRP > 10 mg/L)	Nonelevated CRP group (CRP ≤ 10 mg/L)	p value
Number	116	124	
Age, n (%)			0.06
60–69	13 (11.2%)	28 (22.6%)	
70–79	52 (44.8%)	48 (38.7%)	
≥80	51 (44%)	48 (38.7%)	
Sex; Female, n (%)	86 (74.1%)	100 (80.6%)	0.29
BMI* (kg/m^2)	22.2 ± 3.8	22.8 ± 3.5	0.23
Preexisting comorbidities			
Hypertension	80 (69%)	83 (66.9%)	0.84
Diabetes	64 (55.2%)	73 (58.9%)	0.65
Number of preexisting comorbidities ≥ 3	41 (35.3%)	50 (40.3%)	0.51
General anesthesia, n (%)	64 (55.2%)	61 (49.2%)	0.43
Cemented type implant n (%)	29 (25%)	28 (22.6%)	0.77
Duration of Foley insertion, d*	4.6 ± 5.7	2.8 ± 4.9	**0.04**
Time interval from injury to operation, d*	4.3 ± 1.4	3 ± 1.4	**0.008**
Blood transfusion (pint)	3.5 ± 2.4	3.2 ± 2.2	0.395
Operation time (min)	103.7 ± 31.8	108.1 ± 31.3	0.252
Preoperative lab*			
WBC	8596.2 ± 2869.1	8374.6 ± 3218.6	0.57
N%	75.7 ± 8.9	73.3 ± 12.3	0.08
ESR	40.1 ± 25.7	25.4 ± 18.4	**<0.0001**
CRP	53 ± 38.2	3.5 ± 6.7	**<0.0001**

*Values are expressed as mean ± standard deviation. BMI, body mass index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; N%, neutrophil count; WBC, white blood cell count; p value estimated using t-test or chi-square test. Values of $p < 0.05$ are displayed in bold.

hypothesis test at an alpha level of 0.05, a power of 0.8, and repeated measures of ANOVA. Repeated measures of ANOVA were used to determine the within-subject effects of time (10 measurements) in two groups (i.e., patients with preoperatively elevated CRP values versus patients with nonelevated CRP values) for ESR and CRP. Sample size calculation was performed using G*Power version 3.1.9.2 [15]. Continuous variables such as WBC, N (%), ESR, and CRP between the two groups (elevated CRP versus nonelevated CRP) were compared using two-tailed t-test. Body weight and height were measured, and BMI was calculated using the formula kg/m^2 and categorized (<25, 25–29, and ≥30). Age was categorized as 60–69, 70–79, and ≥80. Categorical variables (i.e., age and BMI) between the two groups (elevated CRP versus nonelevated CRP) were compared using Pearson's Chi-square test. A generalized estimating equations model was used to analyze for repeated measures of the four markers through 14 days. The significance level was 0.05 in this study. All analyses were performed using R version 3.1.2 [16]. Regression analysis was performed to identify whether there are any significant factors that influence the temporal values of the four markers. Demographic variables included age, sex, BMI, preexisting comorbidities, anesthetic type, cemented versus uncemented prosthesis, and time interval from injury to operation.

3. Results

Demographic characteristics, including preexisting comorbidities, anesthesia type, cemented versus uncemented prosthesis, and time interval from injury to operation, are summarized in Table 1. The mean values with standard deviation of the four inflammatory markers, WBC, N (%), ESR, and CRP, for each time period are shown in Table 3. The above parameters were compared in patients with and without preoperatively elevated CRP, resulting in different kinetic curves only for CRP though an entire sampling day ($p < 0.001$). However, for WBC, N (%), and ESR, GEE analysis with repeated measurements could not determine statistically significant differences through an entire sampling day because of the interaction in time.

For WBC, N (%), and ESR, the two groups showed similar patterns of temporal values 14 days after surgery with no statistically significant differences regardless of preoperative CRP level. Preoperative WBC and N (%) showed no significant differences between the two groups ($p = 0.57$ and $p = 0.08$, resp.), and their kinetic curve patterns were relatively constant with time change (Figures 1 and 2). Preoperative ESR in patients with preoperatively elevated CRP was significantly higher than in those with nonelevated CRP (40.1 ± 25.7 and 25.4 ± 18.4, resp., $p < 0.001$). However, a similar pattern of

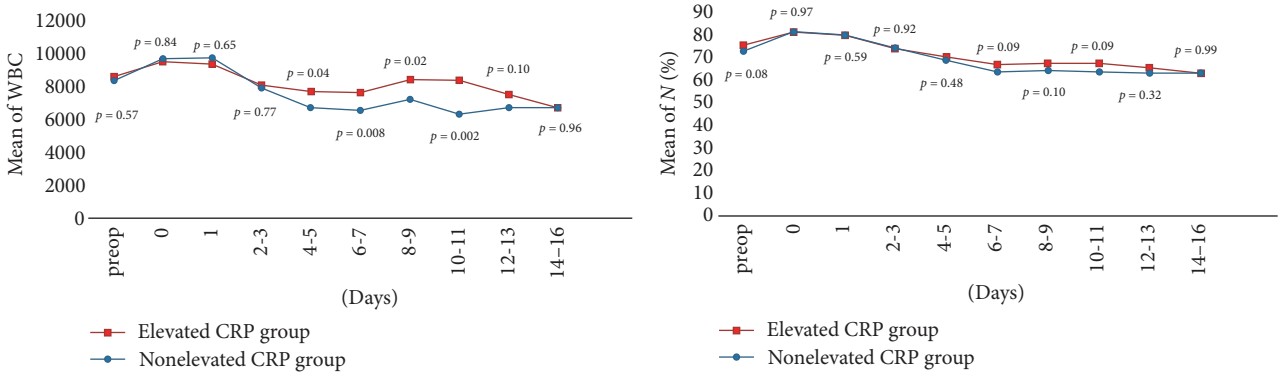

Figure 1: Perioperative WBC and neutrophil count (%) kinetics. p value estimated using t-test at each sampling day.

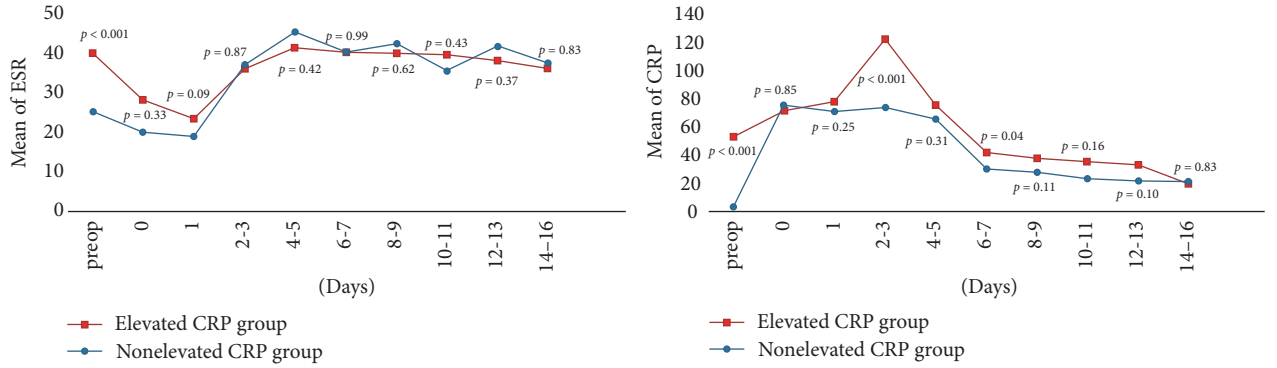

Figure 2: Perioperative ESR and CRP kinetics. p value estimated using t-test at each sampling day.

ESR kinetics, elevated on the 3rd-4th postoperative day with a sustained curve, was observed 14 days after surgery in both groups (Figure 2).

At 48–60 h postoperatively, the mean CRP was markedly higher in patients with preoperatively elevated CRP that in those with nonelevated CRP (122.1 ± 65.9 and 73.7 ± 35.5, resp., $p < 0.001$). CRP kinetics after hip fracture surgery was different in patients with preoperatively elevated CRP compared with in those with nonelevated CRP. The abrupt elevation of CRP in patients with preoperatively elevated CRP was conversely decreased on the 4th-5th postoperative day, demonstrating similar kinetic curves with no significant differences between both groups (Figure 2). The difference in the kinetic curve for perioperative CRP between the two groups was influenced by male gender ($\beta = -17.28$, $p < 0.001$), age ($\beta = 10.05, 7.28$, $p < 0.001$), preexisting comorbidities ≥ 3 ($\beta = -17.28$, $p < 0.001$), and general anesthesia ($\beta = 7.2$, $p < 0.001$); on the other hand, it was not influenced by duration of Foley insertion ($p = 0.18$), cemented versus uncemented prosthesis ($p = 0.39$), time interval from injury to operation ($p = 0.12$), transfusion number ($p = 0.10$), and operation time ($p = 0.87$) (an appendix is available as Supplementary Materials Tables s1–4). The proportion of cases with CRP within normal ranges (<10 mg/L) at 14 days after surgery was lower in the elevated CRP group than in the nonelevated CRP group (38.7% and 59.6%, resp., $p < 0.001$) (Table 2).

4. Discussion

The principal finding of this study was (1) CRP kinetics after hip fracture surgery was different in patients with preoperatively elevated CRP compared with in those with nonelevated CRP (2) There was the abrupt elevation of CRP at 48–60 h postoperatively in patients with preoperatively elevated CRP was conversely decreased on the 4th-5th postoperative day, demonstrating similar kinetic curves with no significant differences between the elevated CRP and the nonelevated CRP groups.

The level of preoperative CRP and the temporal values of CRP and ESR after surgery have been used as guides to determine surgical timing and presence of PJI after surgery [17]. In this study, time interval from injury to operation was significantly longer in elevated CRP group. The wait time before surgery could be increased because of the evaluation of CRP progression or underlying pulmonary or urinary tract infection. However, a delay from injury to operation did not affect the CRP kinetics after operation. This should be noticed and also the delay should be minimized.

CRP level is an important inflammatory marker for developing treatment plans during the follow-up period after arthroplasty [18]. The preoperative level of CRP provides an individual reference level to compare the changes in CRP levels after surgery. However, CRP level can be elevated by intracapsular fractures of the femoral neck from increase

Table 2: The proportion of the hip with the CRP value within normal ranges (<10 mg/L) at 14 days.

At POD 14 days	Elevated CRP group	Nonelevated CRP group	p value
CRP > 10 at postop 14 d	43 (62.3%)	38 (40.4%)	<0.001
CRP ≤ 10 at postop 14 d	26 (38.7%)	56 (59.6%)	<0.001

POD, postoperative day; CRP, C-reactive protein; p value estimated using chi-square test.

in inflammatory factors because of synovial membrane production [19] and correlated with the severity of surgical or traumatic injury [20], underlying patients' conditions such as frailty [3, 4] or rheumatoid arthritis [7].

The reference levels of CRP and ESR have been criticized because of their low specificity for diagnosing infections [21]. Therefore, most surgeons refer to temporal patterns rather than the value at a specific time point [18]. Several studies have investigated CRP kinetics following surgical procedures [22–26]. These studies consistently found that CRP increases after the surgery, peaks on the second day, and then gradually returns to normal around the seventh day. When considering CRP kinetics, White et al. [24, 27] suggested that if the natural CRP kinetics is interrupted by a second rise or is persistently elevated, an infection should be suspected.

An understanding of postoperative CRP kinetics would contribute to the screening and diagnosis of PJI. However, no studies have investigated the changes in temporal values of inflammatory markers in relation to the reference level of preoperative CRP in patients with no infectious complications of pneumonia, urinary tract infection, and PJI. It is essential to rule out postoperative infection for shorter hospital stays after an operation. Therefore, it would be helpful if there are parameters that can function as guidelines to determine infection when deciding patient discharge, as the duration of antibiotic prophylaxis is restricted to not exceed 24 h postoperatively [9]. In this regard, a sensitive marker of CRP that is rapidly detectable might be a valuable and convenient parameter.

A higher peak value of mean CRP was observed 48–60 h postoperatively in patients with elevated preoperative CRP than in the other group, which gradually decreased to baseline levels and patterns within normal ranges around 3-4 days after surgery. In the present study, the proportion of cases with CRP within normal ranges (<10 mg/L) 14 days after surgery was still substantially lower in the elevated CRP group than in the nonelevated CRP group. This finding should be taken into consideration during the follow-up period.

If a sudden rise of CRP in the blood test of patients is confirmed 2-3 days after surgery, surgeons can encounter difficulties. The results of this study might provide a reference for the ongoing blood test with confidence. Our findings would also serve as a reference in determining the duration of prophylactic antibiotic treatment even for patients with preoperatively elevated CRP; a higher preoperative CRP level and a high peak value of CRP postoperatively might be an issue when surgeons decide to discontinue antibiotics treatment.

For WBC, N (%), and ESR, the two groups had similar patterns of time values 14 days after surgery with no statistically significant differences regardless of preoperative CRP level. Preoperative WBC and N (%) were not different between the two groups, and kinetics curves demonstrated relatively constant patterns with a high baseline, probably secondary to an increase in interleukin-6 gene expression and postulated to be related to frailty and predisposition to certain diseases at an advanced age even without signs of illness or inflammation [28].

Lastly, we found several variables affecting the difference in the kinetic curve for perioperative CRP in aged patients having hip fractures with and without elevated preoperative CRP. Male gender, older age, preexisting comorbidities ≥ 3, and general anesthesia were significantly influenced to the difference. Though we could not clarify the reason and did not evaluate other clinical variables such as fracture type, soft tissue damage, and inflammatory disease, the results might be useful to be referred in interpretation of the changes in temporal values of CRP after surgery.

Our study had an inherent limitation because of its retrospective design. Our findings were not able to provide conclusive data on the kinetics of the four inflammatory markers with regard to PJI because this study involved patients with no perioperative infections. This result would be helpful as guidelines for deciding patient discharge and the duration of antibiotic prophylaxis. Another limitation was elevated CRP was set arbitrally to greater than 10 or not even. The normal values of CRP levels were set to less than 0.5 mg/dL [16, 29]. However, CRP level suggesting chronic PJI were generally considered to be more than 10 mg/L [30–32]. Also, the main result of this study was not the threshold of CRP level to determine PJI but natural kinetics of CRP level with no PJI.

The main strength of our study was the large number of patients and its clinical relevance for postoperative blood sampling timing following hip arthroplasty for femoral neck fracture in elderly patients. And the consideration for rather homogenous cohort with only patients with isolated femoral neck fracture underwent bipolar hemiarthroplasty might compensate the statistical weakness.

In conclusion, CRP levels could be used as guidelines for patient discharge and during the follow-up period after surgery but have to be monitored for at least postoperative 14 days with consideration of the differential kinetic curves of perioperative CRP with a different reference level of preoperative CRP.

Abbreviations

CRP: C-reactive protein
ESR: Erythrocyte sedimentation rate
WBC: White blood cell count
N: Neutrophil count
HA: Hemiarthroplasty.

Table 3: The temporal value of the perioperative four inflammatory markers of WBC, *N* (%), CRP, and ESR.

Sampling day	WBC			*N*%			ESR			CRP		
	Elevated CRP group Mean (SD)	Nonelevated CRP group Mean (SD)	*p* value	Elevated CRP group Mean (SD)	Nonelevated CRP group Mean (SD)	*p* value	Elevated CRP group Mean (SD)	Nonelevated CRP group Mean (SD)	*p* value	Elevated CRP group Mean (SD)	Nonelevated CRP group Mean (SD)	*p* value
Preop	8596.2 (2869.1)	8374.6 (3218.6)	0.57	75.7 (8.9)	73.3 (12.3)	0.08	40.1 (25.7)	25.4 (18.4)	<0.001	53 (38.2)	3.5 (6.7)	<0.001
0	9595.9 (3328.5)	9736.8 (6978.9)	0.84	81.6 (7.6)	81.6 (6.6)	0.97	28.2 (24.4)	20.2 (25.3)	0.33	72.1 (52.9)	75.8 (55.6)	0.85
1	9379.4 (2866)	9776.7 (9050)	0.65	80.2 (6.5)	80.6 (5.3)	0.59	23.4 (17.8)	19.1 (17)	0.09	77.7 (38.4)	71 (37.7)	0.25
2-3	8096.7 (2757)	7938.5 (2999)	0.77	74.4 (7.8)	74.5 (9)	0.92	36.1 (24.6)	37.1 (28.2)	0.87	122.1 (65.9)	73.7 (35.5)	<0.001
4-5	7736.8 (2746.9)	6724.9 (2794.2)	0.04	70.5 (9.4)	69.3 (9.7)	0.48	41.4 (23.6)	45.4 (25.9)	0.42	75.3 (51.8)	65.6 (45.1)	0.31
6-7	7661.5 (2783.2)	6618.5 (2196.5)	0.008	67.2 (12.7)	64.1 (10)	0.09	40.3 (26.5)	40.4 (22.3)	0.99	42 (32.6)	30.5 (34.1)	0.04
8-9	8438.3 (3055)	7236.4 (2518.4)	0.02	68 (10.4)	64.6 (11.8)	0.1	39.9 (24.2)	42.3 (24.3)	0.62	38 (37.8)	27.8 (24.8)	0.11
10-11	8399.5 (3692.2)	6378.4 (2058.4)	0.002	67.7 (10.8)	63.7 (11)	0.09	39.7 (24.4)	35.7 (20.2)	0.43	35.7 (40)	23.2 (38.5)	0.16
12-13	7536.3 (2670.5)	6755.5 (2293.8)	0.1	65.9 (9.3)	63.8 (13)	0.32	38.1 (20.2)	41.8 (21.6)	0.37	33.4 (42.1)	21.8 (25.1)	0.1
14–16	6774.5 (2150.6)	6747.7 (2513.3)	0.96	63.6 (11.5)	63.6 (12.6)	0.99	36.3 (27.4)	37.5 (20.8)	0.83	20.4 (23.7)	21.7 (32.5)	0.83

SD; standard deviation; *p* value estimated using *t*-test.

Data Availability

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

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The current study obtained Institutional Review Board approval from our institution (KANGDONG 2016-11-006) before study onset, and our protocol was also approved.

Consent

Informed consent was obtained from all participants.

Disclosure

The manuscript was presented in The 61st Annual Congress of the Korean Orthopaedic Association in 2017.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Dr. Seung-Jae Lim and Byung Hoon Lee participated in the study design and helped to draft the manuscript. Kyung-Hwa Choi as a consultant for statistical analysis performed the statistical analysis. Jin Hyuck Lee, Joon Young Jung, and Woosol Han conceived of the study and participated in its design and coordination and helped to draft the manuscript. All authors participated in the development of and approved the final manuscript and agreed to be accountable for the integrity of the content. Seung-Jae Lim and Jin Hyuck Lee contributed equally to this study.

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Supplementary Materials

Table s1: effect on preoperative WBC through 14–16 days after surgery according to elevated CRP group by generalized estimating equation (GEE) model. Table s2: effect on preop *N*% through 14–16 days after surgery according to elevated CRP group by generalized estimating equation (GEE) model. Table s3: effect on preop ESR through 14–16 days after surgery according to elevated CRP group by generalized estimating equation (GEE) model. Table s4: effect on preop CRP through 14–16 days after surgery according to elevated CRP group by generalized estimating equation (GEE) model. *(Supplementary Material)*

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Review Article

Periprosthetic Joint Infection of Shoulder Arthroplasties: Diagnostic and Treatment Options

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Periprosthetic joint infection (PJI) is one of the most frequent reasons for painful shoulder arthroplasties and revision surgery of shoulder arthroplasties. *Cutibacterium acnes (Propionibacterium acnes)* is one of the microorganisms that most often causes the infection. However, this slow growing microorganism is difficult to detect. This paper presents an overview of different diagnostic test to detect a periprosthetic shoulder infection. This includes nonspecific diagnostic tests and specific tests (with identifying the responsible microorganism). The aspiration can combine different specific and nonspecific tests. In dry aspiration and suspected joint infection, we recommend a biopsy. Several therapeutic options exist for the treatment of PJI of shoulder arthroplasties. In acute infections, the options include leaving the implant in place with open debridement, septic irrigation with antibacterial fluids like octenidine or polyhexanide solution, and exchange of all removable components. In late infections (more than four weeks after implantation) the therapeutic options are a permanent spacer, single-stage revision, and two-stage revision with a temporary spacer. The functional results are best after single-stage revisions with a success rate similar to two-stage revisions. For single-stage revisions, the microorganism should be known preoperatively so that specific antibiotics can be mixed into the cement for implantation of the new prosthesis and specific systemic antibiotic therapy can be applied to support the surgery.

1. Introduction

Periprosthetic joint infection (PJI) of the shoulder joint is a rare but serious complication of shoulder arthroplasties. The mean incidence has been reported to be 1.1%; after reverse arthroplasty, it can be 3.8% and can reach 10% in the subgroup of male, young patient operated on with a reverse prosthesis [1–4]. However, PJI is the most common reason for revisions of shoulder prosthesis made necessary by pain, stiffness, or loosening [5]. Pottinger et al. [6] reported that periprosthetic infections were detected in 56% of 193 shoulder prosthesis revisions. Therefore it is suggested that, until proven otherwise, every report of pain, stiffness, and loosening of the shoulder prosthesis should be regarded as an indication of infection.

Risk factors associated with periprosthetic shoulder infections are posttraumatic osteoarthritis, previous surgery, repeated cortisone injections, systemic corticosteroid treatment and other immunosuppressive medicaments, rheumatoid arthritis, and diabetes mellitus [4, 6, 7]. Richards et al. [5] studied 4,258 patients with shoulder prostheses and found that males were 2.59-times more at risk for infection than females and that reverse total shoulder arthroplasty was associated with a 6.11-higher risk of infection than anatomical shoulder arthroplasty. However, the fact that reverse shoulder arthroplasty is frequently used for revision surgery may cause this difference. Trauma-associated prostheses were associated with a 2.98-greater risk of infection [5].

The microorganisms most commonly associated with periprosthetic infections are the skin pathogens *Staphylococcus* sp. and *Cutibacterium acnes (Propionibacterium acnes)*. Recent studies have shown that the *Cutibacterium acnes (Propionibacterium acnes)* is associated with between 31% and 70% of all periprosthetic shoulder infections and causes many

more periprosthetic infections in the shoulder than in other joints, probably because of the proximity of the surgical site to the axillary region [5, 6, 8].

The classification proposed by Tsukayama et al. [31] differentiates between acute early and chronic late infections whereby the threshold between the two is 4 weeks after the surgical intervention. However, other authors regard infections occurring up to 3 months after surgery as early infections [32–36]. Acute periprosthetic infections that arise after many trouble-free years as a result of an infection at a remote site are classified as acute hematogenous infections and are treated in the same way as acute early postoperative infections [31].

PJI of shoulder arthroplasties have different distributions of microorganisms and are less frequent compared to PJI of hip and knee arthroplasties. Clear and standardized concepts for diagnosis and surgical and antibiotic treatment have not been reported in the literature. Because of this inhomogeneity in diagnosis and treatment, the ASES (American Shoulder and Elbow Surgeons) has formed a special committee for the treatment and diagnosis of PJI. This review presents an overview of different diagnostic and therapeutic options and discussion of their advantages and disadvantages.

2. Diagnostic Methods

It is not only because of the incidence of infection and the difficulties to detect a slow growing pathogen such as *Cutibacterium acnes* that an accurate, preoperative diagnostics have particular importance in cases of loosened or painful shoulder arthroplasties. These diagnostic tests should be carried out before every revision surgery because evidence for a periprosthetic infection results in a significant change in the treatment. A sufficient preoperative diagnostic may also reduce the amount of unexpected positive cultures in revision shoulder arthroplasty which was 23.9% of 117 revision shoulder arthroplasties in the study of Padegimas et al. [37], of which 57.1% were *Cutibacterium acnes*.

The principles involved in the diagnosis of a periprosthetic infection of the shoulder joint do not differ from those used to investigate hip or knee joints, so much of the experience gained from the more frequently performed hip and knee arthroplasties can be used directly for developing diagnostic tools for assessing infections of shoulder prostheses.

Early infections and acute hematogenous infections are usually associated with local and systemic signs of inflammation. Local signs of inflammation are not always obvious, however, because of the amount of soft tissue covering the shoulder joint. A rapid diagnosis can be achieved by determining the level of C-reactive protein in the blood and the leukocyte count in the joint fluid. In this case, the leukocyte count is usually raised to levels much greater than 10,000/μL [38].

Local and systemic signs of inflammation are absent in cases of late periprosthetic infections, so an accurate diagnosis is much more difficult. In 2011, the Musculoskeletal Infection Society proposed a series of criteria for defining periprosthetic infections; these were adapted in 2014 and proposed that an infection definitely exists when one major criterion or at least three of the five minor criteria are met [39].

The major criteria include

(i) evidence for organisms with identical phenotype in at least two positive periprosthetic cultures of aspirated joint fluid and/or synovial tissue samples; or

(ii) a fistula communicating with the prosthesis.

The minor criteria include

(i) elevated erythrocyte sedimentation rate (ESR $\geq$ 30 mm/h) and level of C-reactive protein (CRP $\geq$ 10 mg/l) in the serum,

(ii) elevated leukocyte (WBC) count in the joint fluid or positive reaction by leukocyte esterase test strips,

(iii) elevated percentage of neutrophil granulocytes (PMN $\geq$ 70%) in the joint fluid,

(iv) positive histological assessment of the periprosthetic tissue,

(v) one single positive culture of periprosthetic tissue or fluid.

The existence of a periprosthetic infection should, in our opinion, always be excluded or proven before a revision arthroplasty is carried out because, on the one hand, a specifically targeted systemic and/or local antibiotic therapy can only be designed on that basis and, on the other hand, the antibiotic therapy can be initiated at the time of surgery. Thus, analyses for PJI should be done preoperatively and should not begin during surgery (e.g., tissue biopsy for bacteriological and histological tests or an intraoperative alpha-defensin test). The intraoperative tests are necessary in our opinion to confirm preoperative diagnosis by obtaining at least two concordant cultures. Some surgeons start the identification of microorganisms intraoperatively and use an empirical broad-spectrum antibiotic treatment [1]. Because the microorganisms most commonly associated with periprosthetic infections are the skin pathogens *Staphylococcus* sp. and *Cutibacterium acnes*, broad-spectrum antibiotics will be sufficient in most cases. However, for resistant *Staphylococcus* sp. and for some Gram-negative microorganisms they are not. In these cases, the initiation of a suitable treatment would not be possible until the microorganism had been detected and identified from samples taken intraoperatively, that is, at a time when leaving bacteria in the periprosthetic tissue had already formed a biofilm around the new implant. In addition, it is useful to obtain an exact differentiation of the pathogen and its resistance pattern so that a systemic antibiotic therapy can be planned preoperatively. This information will also enable the addition of specific antibiotics to the cement used in a one-stage or two-stage revision arthroplasty that are tailored to the pathogen concerned [40, 41]. In this way, local and systemic antibiotic treatments can be devised according to the identity and resistance pattern of the infecting pathogen and so avoid the unnecessary, nonspecific use of broad-spectrum antibiotics with all its disadvantages. In addition, this will also reduce the development of resistance to the antibiotics [37, 38, 40, 41].

We divide the currently available diagnostic methods for demonstrating the presence of a periprosthetic infection or its absence into two groups: direct or specific methods for detecting the pathogen and testing its sensitivity to antibiotics, and indirect or unspecific methods that are unable to provide such information. Indirect, unspecific methods only provide evidence or proof of an infection but leave the questions unanswered of the identity of the pathogen and of its antibiotic susceptibility. Thus, with those considerations in mind, we put great value on the application of specific methods (aspiration or biopsy) of assessment before a revision arthroplasty is carried out.

Imaging methods are nonspecific tests. Early implant loosening or osteolyses (2-3 years after the operation) shown in the radiographies are suspicious for PJI [42]. Scintigraphy is not useful in the first postoperative year because of false positive results due to physiological adaptations processes of the bone to the implant [42]. Moreover, they have a low specificity [42]. Leucocyte-scintigraphy does not have higher sensitivity and specificity, and computed tomography (CT) and magnetic resonance tomography (MRT) do not play any role for diagnosing PJI at the shoulder but may be helpful for visualizing abscess formations and positron emission tomography (PET) in combination with CT is indicated for the latter situation [42].

The CRP value in the blood as a nonspecific test is below 10 mg/L in many cases of periprosthetic infections [42]. Dodson et al. [43] found CRP values higher than 10 mg/L in only 72% of periprosthetic shoulder infections. IL-6 has been shown to be specific but not sensitive for PJI [42]. Thus, it is necessary to use other diagnostics methods in order to prove or exclude the existence of a periprosthetic infection before a revision arthroplasty is carried out.

The aspiration of the joint offers different nonspecific and specific tests. The determination of the cell count in the aspirate is one nonspecific test. Moroder et al. [42] established that a cell count of more than 2000/μl and/or more than 70% of polymorph nuclear leucocytes is indicating a late PJI of the shoulder.

Another nonspecific test is the leucocyte esterase strip test. For diagnosis of PJI of total knee and hip arthroplasties, the sensitivity was between 69% and 81% and the specificity between 93% and 100% [44–46]. However, 17% to 30% of the test was nonreadable because of blood contamination of the aspirate. Centrifugation of the aspirate may improve the readability of the aspirates [47].

A new addition to the range of diagnostic nonspecific tools is the alpha-defensin synovial fluid biomarker assay that has become established as an unspecific diagnostic method in recent years. Sensitivity and specificity of the assay have been reported to be between 97% and 100% [48, 49]. Alpha-defensin is released by leukocytes following contact with bacteria and acts as autogenic antimicrobial agent. It has the advantage that, unlike CRP, systemic inflammatory diseases do not affect it and that previous antibiotic administration does not affect its release or the assay [50, 51]. Frangiamore et al. [52] studied shoulder prostheses and reported a sensitivity of 63% for the test and a specificity of 95%.

One of the specific assays for analysis of the bacteria involves the bacteriological cultivation of preoperative joint aspirates [29, 53–55]. Ince et al. [29] reported a sensitivity of 81.2% in the diagnosis of PJI of the shoulder.

A further direct and specific diagnostic method involves biopsy of periprosthetic tissue. Here, the biopsied material is obtained using biopsy forceps via arthroscopic access. At least 5 samples should be taken for bacteriological cultivation and should be added by additional samples for histological examination or frozen sections. The question of whether the tools between each sample should be changed to avoid contamination is not answered in the literature. However, the utility of this basic precaution seems to be obvious.

It is essential to incubate the synovial fluid and biopsy tissue samples for a sufficiently long period, at least 14 days [39, 40, 56, 57]. This extended incubation time is necessary because, on the one hand, the bacteria causing the periprosthetic infection occur at a very low concentration in the biofilm and, on the other hand, are often sessile; these properties lead to a very low growth rate [56, 58–60]. Especially, *Cutibacterium acnes* (in 31% to 70% of the cases the responsible microorganism for PJI of shoulder arthroplasties) is a very slow growing bacterium and needs a long incubation period for its detection [5, 6, 8]. In our study of 110 PJI of hip and knee, we found that only 27% of these slow growing microorganisms were detected after an incubation time of 7 days and that the remaining 73% first showed bacterial growth during the second week of incubation [40]. Dodson et al. [43] also found that evidence for the presence of bacteria in 11 patients with PJI of the shoulder only appeared during the second week of incubation. Moreover, Pottinger et al. [6] reported an incubation time of up to 28 days for *Cutibacterium acnes* in patients with periprosthetic shoulder infections. Therefore for detection of *Cutibacterium acnes,* cultures need to be held for 14 to 21 days. Using the bloodstream infection samples and the automatic detection of culture, the delay is now less than 14 days for almost all the pathogens except few, like *Mycobacteria*.

The synovial tissue can also be analyzed using PCR methods to detect the microorganism. The advantage of PCR is that the result is available after few hours and PCR technique can now detect most antibiotic resistances. A disadvantage is the quite high percentage of false positive results due to the detection of not only living bacteria [56, 61].

The advantage of biopsy is the possibility of combining the different diagnostic methods of cultivation and histological examination on several tissue samples [39, 62, 63]. Dilisio et al. [64] studied 41 shoulder arthroplasties and found that biopsy is more reliable than aspiration of the synovial fluid and could accurately confirm or rule out the presence of an infection. The biopsy method was associated with a sensitivity of 100%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 100%, whereas the aspiration method was found to have a sensitivity of only 16.7%, a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 58.3%. Therefore, we suggest synovial biopsy in cases where the other indirect and direct diagnostic methods did not lead

to a clear decision on periprosthetic infection and could not identify the microorganism.

3. Treatment of Early Infections

The treatment of acute postoperative and hematogenous periprosthetic infections involves a radical surgical debridement of the periprosthetic tissue and a radical synovectomy. This is then followed by a thorough irrigation (also with antiseptic fluids) of the tissue. These are usually open procedures, with the prosthesis inlay being exchanged at the same time. Arthroscopic irrigation does not allow such a radical approach and is associated with lower rates of success than those attained with open debridement and inlay exchange, as seen in the publications of Choi et al. [65] and Byren et al. [66]. Because the onset of infection is often unknown with precision in hematogenous periprosthetic infections, the success rate is lower than in acute postoperative infections [67].

The bacterium causing these infections is mostly unknown at the time of surgery and initiation of the antibiotic therapy. Therefore an empirical antibiotic treatment has to be started until the microorganism is identified and the specific antibiotic therapy can be adapted to the susceptibility of the microorganism. Zimmerli et al. [36] and Trampuz and Zimmerli [68] give great importance to the use of rifampicin for retaining the prosthesis because it is active against nonresistant bacteria in the biofilm. For infected hip and knee arthroplasties, Zimmerli et al. [36] achieved a success rate of 100% in the treatment of 12 periprosthetic infections using a combination of ciprofloxacin and rifampicin; only 58% success was achieved when ciprofloxacin was combined with a placebo for the treatment of a similar number of patients. Berdal et al. [33] reported 82% success with an antibiotic combination of rifampicin and ciprofloxacin for treating 29 patients. An explanation for this success was suggested to be the ability of rifampicin to affect sensitive, sessile, Gram-positive pathogens in the bacterial biofilm [36, 69, 70]. Fluoroquinolones such as ciprofloxacin are effective against Gram-negative bacteria in the early biofilm [69, 71–73]. Thus, Aboltins et al. [32] were successful in treating 15 of 17 postoperative early Gram-negative infections with ciprofloxacin (nine cases of a mixed infection with staphylococci were treated in combination with rifampicin) while Martínez-Pastor et al. [34] noted that treatment with fluoroquinolones was a positive factor in the treatment of 47 patients with Gram-negative infections. In our own study of infected knee and hip arthroplasties, we chose vancomycin as the combination partner for rifampicin for the first days until the microorganism has been identified because a high level of resistance to fluoroquinolones such as ciprofloxacin exists in our own population and in other centres too [67, 74–76]. Aboltins et al. [32] decided on a combination of vancomycin and other antibiotics administered over a mean period of five weeks as the initial intravenous therapy in 9 of 17 cases with mixed Gram-negative and Gram-positive infections. In our own study of infected knee and hip arthroplasties, we achieved a success rate of 82% when treating acute infections in the first days with a combination of rifampicin and vancomycin followed by a specific antibiotic treatment for a whole period of six weeks [67].

There is little or no published information about how long the antibiotic therapy should actually last. While Zimmerli et al. [70] recommend three months for infections of hip endoprostheses and six months for infected knee prostheses, most authors favour continuing antibiotic therapy until the inflammation parameters have normalised. Several factors led to our decision to carry out a standardized therapy of 6 weeks. Firstly, there is no evidence that a prolonged antibiotic treatment has a positive effect on retention of the prosthesis. Secondly, a prolonged antibiotic therapy is more likely to lead to a masking of the infection and a delay in identifying a treatment failure than to prevent it [67]. In our own experience, an early recognition of a treatment failure leads to an earlier revision of the infected prosthesis. Thirdly, the level of resistance to the antibiotic is increased when treatment failure occurs after a prolonged antibiotic administration [77].

4. Treatment of Late Infections

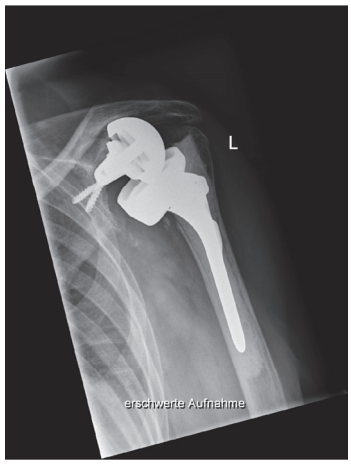
Procedures that can be considered for the treatment of late periprosthetic infections include antibiotic administration alone, debridement of the soft tissue, sine-sine resection arthroplasty, a permanent spacer, and one-stage or two-stage septic revision. Treatment with antibiotics alone is not really an option because the bacteria in the biofilm cannot be eliminated in this way. This was the reason for Coste et al. [10] observing a reinfection rate of 60%. Simple removal of the infected prosthesis and conversion to a sine-sine resection arthroplasty resulted in an improved reinfection rate of 30% according to Coste et al. [10] and even of 0% as reported by Romanò et al. [17]. However, joint function following sine-sine resection arthroplasty is considered to be poor [12, 17] (Table 1).

5. Permanent Spacer

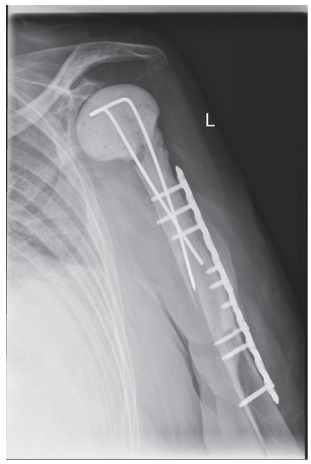
The implantation of a spacer after removal of the infected prosthesis results in a very much better joint functionality. Some authors leave the implanted spacer permanently in position and achieve reproducibly low levels of reinfection, even down to 0%, and a satisfactory joint function (Table 2). The spacer acts as a depot for an antibiotic and releases it into the infected prosthesis bed whereby the local concentration of the antibiotic active substance is very much higher than that achievable by systemic administration of the drug. It is also possible to prepare a tailor-made antibiotic/cement mixture, based on the specific resistance and sensitivity pattern of the pathogen concerned. The spacer also maintains the correct tension in the soft tissues and preserves the length of the arm, which in turn leads to better functionality (Tables 1 and 2).

6. Two-Stage Revision

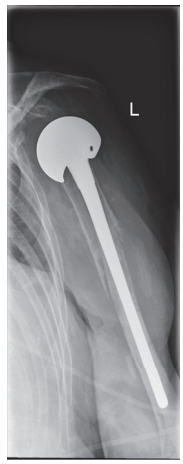
Two-stage revision surgery is the most common method for treating infected prostheses (Figures 1(a)–1(c)). A general



(a) Periprosthetic joint infection of an inverse shoulder arthroplasty on the left shoulder of a 75-year-old woman 3 years after implantation with a loose glenosphere and glenoidal bone defect and a stable shaft implant



(b) Spacer at the left shoulder after removal of the infected inverse shoulder arthroplasty with plate osteosynthesis because of periprosthetic fracture during the stem removal



(c) Reimplantation of a revision stem in the second stage with a big head because of the glenoidal bone defect which excludes a reimplantation of the glenosphere

Figure 1

Table 1: Resection arthroplasty.

Authors	*N*	Follow-up (years)	Systemic antibiotic treatment	Freedom from infection (%)	Score
Braman et al. 2006 [9]	7	1.7		100	
Coste et al. 2004 [10]	10	2.8	No information	70	30 CS
Rispoli et al. 2007 [11]	13	8.3	No information	100	
Sperling et al. 2001 [12]	21			71.4	
Debeer et al. 2006 [13]	7	0.9			26 CS
Verhelst et al. 2011 [14]	11	1.9			46 CS
Ghijselings et al. 2013 [15]	6	2.1			28 CS
Weber et al. 2011 [16]	5	4		100	33 CS
Romanò et al. 2012 [17]	6	3.5		100	32 CS

Table 2: Permanent spacer.

Authors	*N*	Follow-up (years)	Systemic antibiotic treatment	Local antibiotic treatment	Freedom from infection (%)	Score
Coffey et al. 2010 [18]	4	1.8		Gentamicin	100	57 CS
Coste et al. 2004 [10]	3	2.8	No information	No information	100	38 CS
Jerosch and Schneppenheim 2003 [19]	2				100	
Themistocleous et al. 2007 [20]	4				100	
Stine et al. 2010 [21]	15	2.4			100	50 DASH
Ghijselings et al. 2013 [15]	4	3.3				21 CS
Romanò et al. 2012 [17]	15	3			93.3	34 CS
Mahure et al. 2016 [22]	9	4			100	57 ASES

Table 3: Two-stage revision.

Authors	*N*	Follow-up (years)	Systemic antibiotic treatment	Local antibiotic treatment	Freedom from infection (%)	Score
Coffey et al. 2010 [18]	12	1.8		Gentamicin	100	57 CS
Coste et al. 2004 [10]	10	2.8	No information	No information	60	35 CS
Cuff et al. 2008 [23]	10				100	
Jerosch and Schneppenheim 2003 [19]	8				100	
Mileti et al. 2004 [24]	4	7.4			100	
Seitz Jr. and Damacen 2002 [25]	5	4.8			100	
Sperling et al. 2001 [12]	3				100	
Stine et al. 2010 [21]	12	2.4			100	
Strickland et al. 2008 [26]	19				63.2	
Weber et al. 2011 [16]	4	4			100	40 CS
Romanò et al. 2012 [17]	17	3.8			100	38 CS
Buchalter et al. 2017 [27]	19	5.25			78	69 ASES
Li et al. 2016 [28]	8	1.65			100	53 CS

advantage of the two-stage concept is that surgical debridement is carried out twice, whereby the second operation enables the eradication of residual organisms remaining after the initial debridement. Since the cement of a spacer is not used for permanent fixation of an implant, the mechanical quality of the cement is not of primary importance and a higher proportion of antibiotic can be added to the cement. It has been possible to achieve a survival rate using two-stage revision concepts for infected shoulder arthroplasties of between 60% and, most commonly, 100% (Table 3). By reducing contractures, the reimplantation of a prosthesis during a two-stage revision procedure is technically easier than after a sine-sine resection arthroplasty (Table 3). Since the rotator cuff is often insufficient following debridement, it is recommended that a reverse shoulder prosthesis be reimplanted. Using this concept, Li et al. [28] achieved a median Constant score of 53.

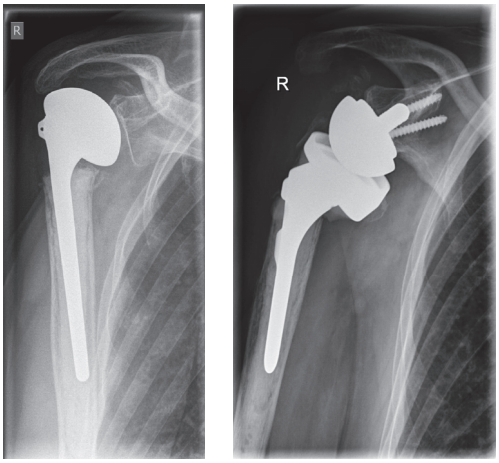
Most studies use the same antibiotic mixed into the cement of the spacer or provided in the industrially preformed spacer [78]. Some authors use vancomycin and tobramycin as local antibiotics on a regular basis because they have a broad spectrum of activity [79]. However, not all bacteria can be successfully treated with these agents (e.g., some Gram-negative organisms), so this is an argument for investigating the antibiotic resistance pattern of the isolated bacteria and selecting a specific antibiotic for the treatment.

An alternative procedure involves antibiotic-releasing beads. A disadvantage of this method is that it is only possible to use industrially prepared beads and they only contain gentamicin or vancomycin. Moreover, arm shortening and instability occur and mobilization becomes very difficult. This in turn usually makes reimplantation of a prosthesis much more difficult because of scarring, tissue contraction, and disuse osteoporosis. In addition, particles of zirconium dioxide abraded during mobilization could lead to third-body-wear damage to the reimplanted prosthesis.

7. One-Stage Revision

The advantage of the one-stage revision is that only one operation is required (Figures 2(a) and 2(b)). On the other hand, functional problems with a sine-sine resection arthroplasty and associated arm shortening and instability, as well as potential spacer fracture, abraded cement particles from the spacer, or bone resorption resulting from the presence of the spacer, can be avoided. In most cases, antibiotic-impregnated cement is used for the reimplantation whereby the antibiotic that is added to the cement or is already contained in it is specific for the pathogen concerned [29, 30]. Even though the preoperative identifying of the pathogen in aspirated synovial fluid or tissue biopsy is not fully satisfactory, for one-stage procedure it is helpful to know the pathogens and their susceptibility to antibiotics. Only then can a specific antibiotic mixture be added to the bone cement and enable a local antibiotic therapy [29, 30]. Recent studies using this concept have achieved infection-free survival of between 90% and 100% (Table 4).

The functional outcomes of one-stage revisions depend on the integrity of the rotator cuff following debridement and the type of prosthesis used (Table 4). Ince et al. [29] achieved a Constant score of 33.6 but only implanted one reverse shoulder prosthesis in a cohort of 16 patients. Klatte et al. [30] showed that the reverse shoulder prosthesis, with a Constant score of 61, was very much better than the bipolar head prosthesis with a Constant score of 56 or a hemiarthroplasty with a Constant score of 43. A study of one-stage revision by Beekman et al. [1] provided support for these data with a Constant score of 55.6%.



(a) Periprosthetic joint infection of a hemiarthroplasty implanted because of a 4-part fracture of the humeral head in a 76-year-old patient with rotator cuff deficiency

(b) Inverse shoulder arthroplasty implanted in a septic one-stage revision

Figure 2

Table 4: One-stage revision.

Authors	*N*	Follow-up (Years)	Systemic antibiotic treatment	Local antibiotic treatment	Freedom from infection (%)	Score
Coste et al. 2004 [10]	3	2.8	No information	No information	100	66 CS
Cuff et al. 2008 [23]	7				100	
Ince et al. 2005 [29]	16	5.7			100	33,6 CS
Sperling et al. 2001 [12]	2				50	
Beekman et al. 2010 [1]	11	0.9			90,9	51 CS
Klatte et al. 2013 [30]	35	2.7			94	51 CS

Nelson et al. [80] and Cuff et al. [23] did not observe any difference in the level of eradication observed after one-stage and two-stage revisions. George et al. [81] undertook a systematic search of relevant publications and found significantly better clinical outcomes after one-stage revisions (mean Constant score of 51) than after two-stage revisions (mean Constant score of 44). In the same report, treatments involving a permanent spacer achieved a mean Constant score of 31 and the sine-sine resection arthroplasty a mean Constant score of 32. The rates of eradication of infection were similar for all four procedures (86.7% for the sine-sine resection arthroplasty, 94.7% for the one-stage revision, 90.8% for the two-stage revision, and 95.6% for the permanent spacer). These results support the concept of the one-stage revision if the pathogen has been characterized.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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