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Review Article

Prevalence, risk factors, microbiological results and clinical outcome in unexpected positive intraoperative cultures in unclear and presumed aseptic hip and knee revision arthroplasties – A ten-year retrospective analysis with a minimum follow up of 2 years

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ABSTRACT

Background: The aim of this study was to assess the prevalence, microbiological spectrum, risk factors, and clinical outcomes of unexpected-positive-intraoperative-cultures (UPIC) in presumed aseptic and unclear revision-total-hip-/knee-arthroplasties (rTHA and rTKA) compared to culture-negative (CN) revisions.
Methods: This study reviewed all International-consensus-meeting-2018 (ICM 2018) negative or inconclusive rTHA (n = 751) and rTKA (n = 679) performed at our institution from 2011 to 2020 with a minimum follow-up of two years. A Kaplan-Meier-analysis was performed to determine the septic and aseptic-free implant survival in cases with UPIC's and matched culture-negative cases. Patient demographics, risk factors, microbiological spectrum and clinical outcomes were evaluated.
Results: There were significantly more UPIC cases in rTHA 196/751 (26.1 %) compared to rTKA 113/679 (16.6 %); ($p < 0.001$). UPICs in rTKA and rTHA have a lower septic and aseptic implant-free-survival compared to CN revisions. Patients with a history of nickel allergy have a higher risk of an UPIC in rTHA and rTKA ($p < 0.001$). Septic re-revisions after UPIC had a significantly (H: $p = 0.004$; K: $p = 0.030$) shorter time period to the primary/previous surgery (H: 84 (IQR:41–797); K: 115 (IQR:55–446)) compared to patients with aseptic re-revisions after UPIC (H:1248 (IQR:178-3534); K: 827 (IQR:361-1183)).
Conclusion: UPICs have a higher rate of septic and aseptic failure than CN outcomes. UPICs are twice as common in rTHA compared to rTKA. Preoperative PJI workup reduces the UPIC rate. Nickel allergy is a risk factor for UPIC. Early revisions with UPICs after primary THA or TKA have a higher risk of septic failure.
The translational potential of this article: This article provides new information on revision rates for UPIC and potential risk factors for UPIC and its treatment failure.

1. Introduction

Besides infection, the most common causes for revision total hip (rTHA) and knee (rTKA) are loosening, wear, instability, or dislocation [1–3]. In aseptic loosening, there is a concern that low-grade PJI may have been the underlying cause of failure [4]. In presumed aseptic rTHA and rTKA unexpected positive intraoperative culture/s (UPIC) are commonly encountered [5,6]. UPICs are often associated with low-virulent pathogen, however there are conflicting data regarding the clinical relevance and management of UPIC [5,7–12]. While some studies have shown that pathogen-detection in presumed aseptic revisions does not affect implant survival [5,12–15], others have shown higher revision rates [9,16–18]. Moreover, a contamination is also a possible cause for a UPIC and cannot be excluded [4,19].

Preoperative joint aspiration and microbiological analysis of periprosthetic synovial fluid has known limitations in detecting pathogens, especially in low-grade infections. Moreover, in some cases, the preoperative PJI workup is inconclusive [20]. These patients do not have clear signs of infection but also cannot be classified as clearly aseptic. In these unclear cases, the treatment algorithm is difficult because over- and

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undertreatment should be avoided [21]. PJI cannot be excluded in patients who do not meet the ICM (International-consensus-meeting) definition [9]. However, the prevalence and clinical outcomes of aseptic and septic re-revision after UPICs or culture-negative (CN) cases in rTHA and rTKA differ between studies, and no clear risk factors have been identified in the literature.

The aim of this study was to evaluate preoperatively presumed aseptic or unclear rTHA and rTKA with ICM-2018 negative or inconclusive criteria. Moreover, we are looking for some results that have an impact on the decision-making process of rTHA and rTKA. We described the septic and aseptic free implant survival in rTHA and rTKA with UPICs and CN results. We also identified certain risk factors for UPICs and their failure, and evaluated the microbiological spectrum in UPICs and septic failures.

2. Material and methods

This retrospective cohort study was approved by the institutional review board (EK11/2020). We analysed our institutional arthroplasty registry and prospectively maintained PJI infection database of our tertiary care academic centre between January 1st 2011 and December 31st 2020. All presumed aseptic and inconclusive revisions were included in this study. Revisions included single-stage exchange, mobile or one- or two-component replacements, hemi-to total arthroplasty, patellar resurfacing, open reduction and internal fixation (ORIF), rTHA or rTKA with intraoperative culture sample(s) (Fig. 1).

Revisions were excluded if (1) PJI was known or suspected preoperatively, (2) the revision was part of the management of an ongoing PJI (second stage of a two-stage revision), or (3) intraoperative cultures were not obtained or results were not available.

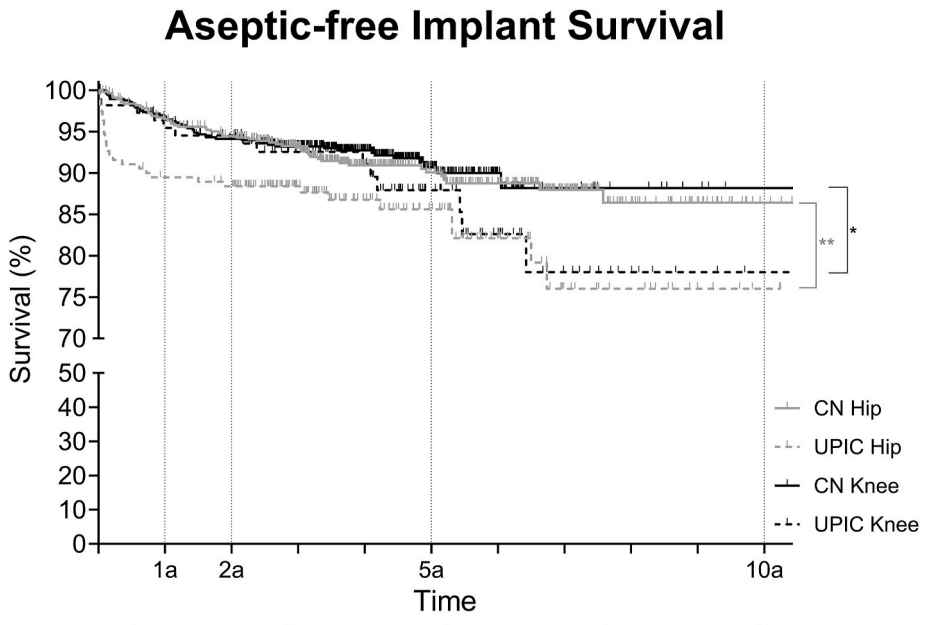
The minimum follow-up was 24 months after the UPIC revision. Follow-up was performed by patient recall, review of our clinical databases for clinical visits, review of the Austrian electronic health record (ELGA) launched in 2015, and review of our death registry. From 2011 to 2015, only re-revisions from our institution were included.

We analysed the outcome between UPICs (Revisions with at least one positive microbiological result) and CNs (Revisions with a negative microbiological result) revisions by evaluating the septic (Procedures due to PJI) and aseptic (Procedures for any aseptic reason) re-revision rates, and the microbiological spectrum. Patient demographics, patient-specific risk factors and reason for revision and re-revision were assessed. Moreover, the causative pathogen(s) of PJI, knee or hip joint, and revision after primary or revision surgery were analysed.

Preoperative evaluation was performed by using serum C-reactive protein (CRP), leukocyte count, synovial fluid CRP, cell-count, and polymorphonuclear leukocyte (PMN) count. The number of preoperative joint aspirations increased over the study period, but was relatively low at the beginning of our retrospective analysis. Patients were preoperatively categorized according to the ICM-2018 criteria. The ICM 2018 PJI score was used to classify all included revisions as inconclusive (3–5) or as non-infected (<3) [22].

All patients received routine intravenous second-generation cephalosporin or vancomycin for those with a history of allergy to penicillin or cephalosporins. Tissue samples or swabs were taken intraoperatively and explanted devices were subjected to sonication as previously described [23]. Microbial identification and antimicrobial susceptibility testing were performed by LABCON GmbH (Austria).

Descriptive statistics were used with means, standard deviations and medians for continuous study parameters and frequencies and percentages for categorical variables. When data were skewed, the interquartile range (IQR) was used. Continuous data were compared using Mann–Whitney U tests or 2-sample t-tests for non-parametric and parametric data, respectively. Categorical data were compared using Pearson's chi-squared test or Fisher's exact test, as appropriate. The Kaplan–Meier method with 95 % confidence intervals (CI) was used to determine septic- and aseptic-free implant survival at 1, 2, 5 and 10 years for the UPIC and CN study cohorts, with subsequent septic or aseptic revision as the end point. Patients who died or were lost to follow-up after 2 years were censored. The 95 % CIs were calculated using the Greenwood's asymmetric exponential formula. Statistical significance was 2-tailed and set at a P-value $\leq$0.05. All analyses were performed using IBM® SPSS® version 25 and GraphPad PRISM® version 8.



Survival (%)	1a	2a	5a	10a	p-value
CN Hip	96.5% (97.5-97.8)	94.1% (95.8-91.7)	90.1% (92.5-86.9)	86.4% (90.3-81.1)	0.010**
UPIC Hip	89.5% (93.1-84.2)	88.4% (92.2-82.9)	85.6% (90.2-79.1)	76.0% (84.7-63.6)	
CN Knee	96.6% (97.8-94.8)	94.1% (95.8-91.8)	90.7% (93.1-87.4)	88.2% (92.1-82.5)	0.244*
UPIC Knee	95.4% (98.1-89.4	93.6% (96.9-87.0)	87.9% (93.3-78.8)	78.0% (87.9-62.1)	

Figure 1. Aseptic free implant survival after 1a, 2a, 5a and 10a (95%-Confidence-interval); a (years), CN (culture negative), UPIC (unexpected positive intraoperative cultures.

3. Results

3.1. Septic and aseptic implant free survival

A total of 751 rTHA and 679 rTKA patients were evaluated. There were significantly more UPIC cases in rTHA 196/751 (26.1 %) compared to rTKA 113/679 (16.6 %); ($p < 0.001$). We observed a lower preoperative aspiration rate in rTHA 18/196 (9.2 %) compared to rTKA 46/113 (40.7 %); $p < 0.001$. UPICs in rTKA and rTHA have lower 1-, 2-, 5- and 10-year septic and aseptic implant-free survival compared to CN revisions (Figs. 1 and 2).

Aseptic failures were significantly higher in UPIC rTHA 15/59 (25.4 %) with previous revisions compared to UPIC rTHA 14/137 (10.2 %) after primary ($p = 0.006$). There was no significant distribution of aseptic failure in rTKA between UPIC after primary and UPIC after previous revisions ($p = 0.392$). There was no significant distribution of septic failure for rTHA and rTKA between UPIC after primary and UPIC after previous revisions (H: p= > 0.99; K: $p = 0.370$). Furthermore, there was no significantly higher septic (H: $p = 1.00$; K: $p = 0.618$) or aseptic (H: $p = 0.186$; K: $p = 0.680$) failure rate in ICM-2018 non-infected or inconclusive patients (Table 1).

3.2. Risk factors for UPIC

There is a significantly (<0.001) higher rate of single-stage exchange and a significantly (<0.001) lower rate of single-component exchange in UPIC rTKA compared to rTHA. Patients with a history of nickel allergy have a higher risk of UPIC outcomes in rTHA and rTKA ($p < 0.001$) (Tables 2 and 3).

3.3. Reasons for failure after UPIC revision

Patients with septic re-revision after UPIC had a significantly (H: $p = 0.004$; K: $p = 0.030$) shorter time period to the primary/previous surgery (H: 84 (IQR: 41–797); K: 115 (IQR: 55–446)) compared to patients with aseptic re-revision after UPIC (H: 1248 (IQR: 178-3534); K: 827 (IQR: 361-1183)) in both rTHA and rTKA.

There were significantly ($p < 0.001$) more consecutive revisions in rTHA 45/196 (22.9 %) compared to rTKA 4/113 (3.5 %). Overall, 7/45 (15.6 %) conversion rTHA and 6/151 (3.9 %) planned rTHA had a septic re-revision ($p = 0.012$). In addition, 1/4 (25 %) of conversion rTKA and 7/109 (6.4 %) of planned rTKA had septic re-revisions ($p = 0.258$) (Table 1).

3.4. Number of culture positive results

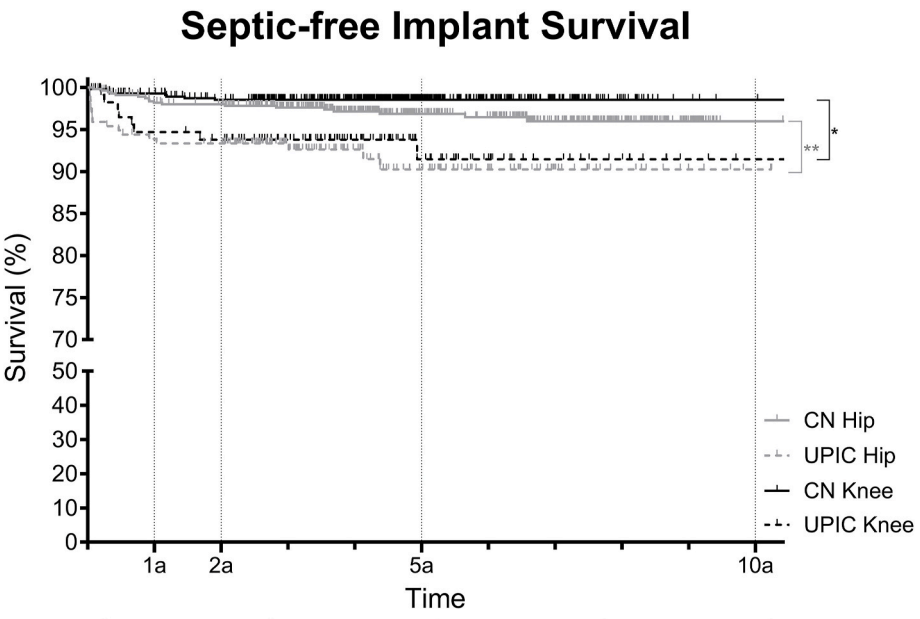
UPICs with ≥2 positive intraoperative cultures with the same microorganism had a significantly higher risk of septic re-revision in rTKA (≥2 culture positive: 3/15 (20 %) compared to single culture positive rTKA 4/98 (4.1 %); $p = 0.048$). This was not the case in rTHA (≥2 culture positive: 3/38 (7.9 %) compared to single culture positive rTKA 10/157 (6.4 %); $p = 0.720$). In these cases, all patients received postoperative antibiotic treatment (Table 1).

3.5. Antibiotic treatment

In total, 44/196 (22.4 %) rTHA and 23/113 (20.4 %) rTKA with UPIC results received postoperative antibiotic treatment for at least two weeks. All other patients started treatment after the third postoperative day for a duration of less than two weeks (H: 92/196 (46.9 %); K: 44/113 (38.9 %)) or received no antibiotic treatment (H: 60/196 (30.6 %); K: 45/113 (53.1 %)). There was no significant distribution for septic or aseptic revision in patients with or without or inadequate antibiotic treatment in rTHA and rTKA. Patients with ICM-2018 for non-infected (H: 100/155 (65.8 %); 53/97 (54.6 %)) compared to ICM-2018 for inconclusive (H: 36/41 (90.2 %); K: 14/16 (87.5 %)) received significantly less antibiotic treatment postoperatively (H: $p = 0.004$; K: $p = 0.013$) (Table 1).

3.6. Virulence of causative pathogen

There were more septic re-revisions in rTHA in patients with high-



Survival (%)	1a	2a	5a	10a	p-value
CN Hip	98.2% (99.0-96.6)	97.8% (98.7-96.1)	96.8% (98.1-94.9)	96.0% (97.5-93.4)	<0.001**
UPIC Hip	93.9% (96.5-89.5)	93.4% (96.1-88.8)	90.2% (94.1-84.0)	90.2% (94.1-84.0)	
CN Knee	99.3% (99.7-98.1)	98.5% (99.3-97.1)	98.5% (99.3-97.1)	98.5% (99.3-97.1)	<0.001*
UPIC Knee	94.7% (97.6-88.6)	93.8% (97.0-87.4)	91.5% (95.9-82.5)	91.5% (95.9-82.5)	

Figure 2. Septic free implant survival after 1a, 2a, 5a and 10a (95%-Confidence-interval); a (years), CN (culture negative), UPIC (unexpected positive intraoperative cultures.

Table 1
Baseline demographics, and operative data for revision total hip and knee arthroplasty with UPIC (unexpected positive intraoperative results). ICM-2018 (International Consensus Meeting-2018), SSI (Surgical Site Infections), CCI (Charlson Comorbidity Index), CRP (C-reactive protein), AB (antibiotic) treatment for at least 2 weeks; *<0.05; **<0.001.

Baseline, demographic, and operation data for revision total hip and knee arthroplasties with UPICs

Variables	Hip	Knee	p-value
	n = 196/751 (26.1 %)	n = 113/679 (16.6 %)	
BMI	28.5 (±6.1)	30.4 (±6.1)	0.021*
Age	71 (25; 90)	71 (41; 88)	0.239
Gender male	72 (36.7 %)	32 (28.3 %)	0.136
female	124 (63.3 %)	81 (71.7 %)	
SSI (0–35)	5.5 (±2.9)	4.4 (±2.6)	0.015*
CCI (0->5)	3.4 (±2.3)	3.5 (±1.6)	0.956
Preoperative aspiration	**18 (9.2 %)**	**46 (40.7 %)**	**<0.001****
Synovial cell-count (10^9)	1.5 (±2.1)	1.0 (+0.9)	0.632
Synovial PMN (%)	45.4 % (±22.2)	35.3 % (±12.3)	0.150
Synovial CRP (mg/l)	1.8 (±2.5)	1.3 (±1.3)	0.919
Serum Cell-count 10^9/l	8.5 (±5.1)	7.6 (±3.1)	0.577
Serum CRP (mg/l)	6.6 (±6,1)	5.0 (±4.7)	0.517
Time to primary/previous revision	2191 (±3899)	2212 (±3923)	0.890
AB treatment postoperatively	**136/196 (69.4 %)**	**67/113 (59.3 %)**	**0.072**
After primary	**137 (68.9 %)**	**84 (74.3 %)**	**0.405**
Septic failure	9/137 (6.6 %)	4/84 (4.8 %)	0.579
Aseptic failure	14/137 (10.2 %)	7/84 (8.3 %)	0.523
After a previous revision	**59 (31.1 %)**	**29 (25.7 %)**	**0.405**
Septic revision	**4/59 (6.8 %)**	**3/29 (10.3 %)**	**0.680**
Septic failure	0/4	2/3 (66.7 %)	0.143
Aseptic failure	2/4 (50.0 %)	0/3	0.429
Aseptic revision	**55/59 (93.2 %)**	**26/29 (89.7 %)**	**0.680**
Septic failure	4/55 (7.3 %)	1/26 (3.8 %)	>0.99
Aseptic failure	13/55 (23.6 %)	4/26 (15.4 %)	0.395
ICM-2018 Not-infected	**155 (79.1 %)**	**97 (85.8 %)**	**0.140**
AB treatment postoperatively	100/155 (65.8 %)	53/97 (54.6 %)	0.118
Septic failure	11/155 (7.1 %)	5/57 (8.7 %)	0.682
Aseptic failure	26/155 (16.8 %)	10/57 (17.5 %)	0.895
ICM-2018 Inconclusive	**41 (20.3 %)**	**16 (14.2 %)**	**0.140**
AB treatment postoperatively	36/41 (90.2 %)	14/16 (87.5 %)	>0.99
Septic failure	2/37 (5.4 %)	2/14 (14.3 %)	0.300
Aseptic failure	3/37 (8.1 %)	1/14 (7.1 %)	>0.99
Single/multiple culture positive	**157 (80.1 %)**	**98 (86.7 %)**	**0.140**
AB treatment postoperatively	105/157 (66.9 %)	54/98 (55.1 %)	0.059
Septic failure	10/157 (6.4 %)	4/98 (4.1 %)	0.435
Aseptic failure	26/157 (16.6 %)	10/98 (10.2 %)	0.156
≥2 Culture positive	**39 (19.9 %)**	**15 (13.3 %)**	**0.140**
AB treatment postoperatively	31/39 (79.5 %)	13/15 (86.7 %)	0.708
Septic failure	3/39 (7.7 %)	3/15 (20.0 %)	0.331
Aseptic failure	3/39 (7.7 %)	1/15 (6.7 %))	>0.99
High-virulent microorganisms	**25 (12.8 %)**	**20 (17.7 %)**	**0.235**
AB treatment postoperatively	20/25 (80.0 %)	13/20 (65.0 %)	0.258
Septic failure	3/25 (12.0 %)	0/20	0.242
Aseptic failure	5/25 (20.0 %)	1/20 (5.0 %)	0.205
Low-virulent microorganisms	**171 (87.2 %)**	**93 (82.3 %)**	**0.235**
AB treatment postoperatively	116/171 (67.4 %)	55/93 (59.1 %)	0.158
Septic failure	10/171 (5.9 %)	7/93 (7.5 %)	0.564
Aseptic failure	24/171 (14 %)	10/93 (10.8 %)	0.447
Reason for revision	196	113	

Table 1 (*continued*)

Baseline, demographic, and operation data for revision total hip and knee arthroplasties with UPICs

Variables	Hip	Knee	p-value
	n = 196/751 (26.1 %)	n = 113/679 (16.6 %)	
Single-stage exchange	**21 (10.7 %)**	**73 (64.6 %)**	<0.001**
Aseptic loosening	16	38	
Dislocation/Instability	3	24	
Pain	—	4	
Malpositioning/ Malaligment	1	4	
Wear	—	2	
Other	1	1	
Mobile part exchange	**33 (16.8 %)**	**15 (13.3 %)**	0.405
Wear	15	3	
Dislocation/Instability	13	8	
Other	5	4	
Cup/Femoral component exchange	**83 (42.3 %)**	**2 (1.8 %)**	<0.001**
Aseptic loosening	61	2	
Disclocation	15	—	
Cup Protrusio	4	—	
Implant failure	2	—	
Wear	1	—	
Stem/Tibial component exchange	**47 (24 %)**	**5 (4.4 %)**	<0.001**
Aseptic loosening	42	5	
Dislocation	3	—	
Fracture	2	—	
Single stage + ORIF	**9 (4.6 %)**	**2 (1.8 %)**	0.197
Hemi- to Total-arthropalsty	**3 (1.5 %)**	**7 (6.2 %)**	0.041*
Patella resurfacing	**-**	**9 (8 %)**	—

virulent 3/25 (12 %) compared to low-virulent 10/171 (5.9 %) microorganisms, but this was not significantly higher (p = 0.100). However, patients with high-virulent microorganisms (H:20/25 (80 %); K:15/20 (75 %)) received antibiotics more often than patients with low-virulent microorganisms (H:110/172 (63.9 %), K:55/93 (59.1 %)) (Table 1).

3.7. Microbiological result

A total of 309 UPICs were evaluated in revision total knee and hip arthroplasties (Table 2). All intraoperative microbiological results are shown in Table 2. There was no significant distribution in the type of previous revision. Furthermore, septic revision prior to UPIC revision did not have significantly higher septic re-revisions rate in our cohort (p = 0.053). The mean number of intraoperative cultures was 3.4 (±2.4) for rTHA and 3.5 (±2.4) for rTKA. All microbiological results were analysed, including swabs, sonication and tissue samples. Almost 98 % of the swabs were collected between 2011 and 2017, while 64.6 % of the tissue samples were collected between 2017 and 2020. We compared the microbiological spectrum of patients with UPIC revisions with the spectrum of the septic re-revisions after UPIC in the same patients. In 10/13 (76.9 %) septic rTHA after UPIC revision and 5/7 (71.4 %) septic rTKA after UPIC revision we found a positive intraoperative result. Interestingly, when we found the same microorganisms (rTHA 4/10 (40 %); rTKA 4/5 (80 %)), they showed a different antibiogram and gained resistance to antibiotics. Three additional microorganisms and six other microorganisms were found in culture-positive re-revisions compared to the previous UPIC results.

4. UPICs in revision total hip arthroplasty

In this study, a total of 751 presumed aseptic/unclear rTHA were evaluated. There were 196/751 (26.1 %) UPIC and 555/751 (73.9 %) CN results. UPIC revisions had a significant higher rate of successful ultrasound guided taps preoperatively compared to CN revisions (p = 0.003). Preoperative visible effusion on ultrasound may correlate with

Table 2
Microbiological spectrum for unexpected positive intraoperative cultures in revision total hip and knee arthroplasties. Strep (Streptococcus), Staph. (Staphylococcus), MSSE (Methicillin-susceptible Staph. epidermidis); MRSE (Methicillin-resistant Staph. epidermidis), MRSA (Methicillin-resistant Staph. Aureus), VRE (Vancomycin-resistant Enterococci), MRGN (Multiresistant-gram negative).

Microbiological spectrum for unexpected positive intraoperative cultures in revision total hip and knee arthroplasties			
Total unexpected positive results	Total n = 309	Hip n = 196 (63.4 %)	Knee n = 113 (36.6 %)
Total number of analyzed cultures	1.039	649	390
Positive rate	438 (42.2 %)	292 (45 %)	146 (37.4 %
Monomicrobial	264 (85.4 %)	165 (84.2 %)	99 (87.6 %)
Polymicrobial	45 (14.6 %)	31 (15.8 %)	14 (12.4 %)
UPIC from swab sample	188 (60.8 %)	115 (58.7 %)	73 (64.6 %)
UPIC from sonication sample	43 (13.9 %)	30 (15.3 %)	13 (11.5 %)
UPIC from tissue sample	48 (15.5 %)	26 (13.3 %)	22 (19.5 %)
UPIC from combined samples	30 (9.7 %)	25 (12.8 %)	5 (4.4 %)
Number of detected microorganisms	337	210	127
Gram positive Bacteria	308 (91.4 %)	194 (92.4 %)	114 (89.8 %)
Staphylococcus Epidermidis	97	74	23
MSSE	47	28	19
MRSE	52	48	4
Cutibacterium acnes	66	36	30
Cutibacterium avidum	3	3	—
Staphylococcus Hominis	22	15	7
Staphylococcus Capitis	18	11	7
Staphylococcus Haemolyticus	9	5	4
Staphylococcus Lugdunensis	6	3	3
Staphylococcus aureus	3	2	1
MRSA	1	1	—
Staphylococcus Warneri	3	—	3
Other CoNS	9	6	3
Bacillus spp.	22	9	13
Micrococcus spp.	5	4	1
Micrococcus luteus	5	3	2
Enterococcus faecalis	8	6	2
Enterococcus faecium	4	2	2
VRE	2	1	1
alpha-hemolytic *streptococci*	8	4	4
Corynebacterium spp.	5	4	1
Other Gram positive bacteria	16	7	9
Gram negative bacteria	21 (6.2 %)	11 (5.2 %)	10 (7.9 %)
Neisseria spp.	5	3	2
Escherichia coli	3	2	1
3 MRGN	2	2	—
Pseudomonas aeruginosa	2	2	—
Enterobacter cloacae	2	—	2
3 MRGN	1	—	1
Other Gram negative bacteria	9	4	5
Fungi	8 (2.4 %)	5 (2.4 %)	3 (2.4 %)
Candida parapsilosis	7	4	3
Aspergillus spp.	1	1	—

UPIC. Moreover, re-revisions were higher in UPICs compared to CN cases (p = 0.002). Single stage exchange and stem exchange have a higher rate of septic-re-revision after UPIC rTHA compared to other revision reasons. All results between UPIC and CN in rTHA are shown in Table 4.

The area under the curve (AUC) for the time between primary/previous revision and UPIC rTHA with septic revision as the state variable was 0.707 (CI-95 % 0.548-0.865). The cut-off value based on Youdon-index was 682 days. Revisions within 682 days after index surgery have a higher risk of septic re-revision than aseptic re-revision in THA.

Table 3
Baseline demographic, and operative data for revision total hip arthroplasty. Mean with SD (standard deviation), median with IQR (Interquartile-range); UPIC (unexpected positive intraoperative cultures) included presumed aseptic and inconclusive revisions; BMI (Body-Mass-Index); ASA (American Society of Anesthesiologists Classification); CRP (C-reactive protein); PMN (Polymorphonuclear neutrophils); ORIF (open reduction and internal fixation) The number of septic re-revisions after a specific operation is compared with the total number of this procedure; *<0.05; **<0.001.

Baseline demographic, and operative data for revision total hip arthroplasty			
Revision total hip arthroplasties	UPIC n = 196 (26.1 %)	CN n = 555 (73.9 %)	P-value
BMI	28.5 (±6.1)	28.1 (±4.9)	0.865
Age	70 (61; 77)	71 (61; 77)	0.606
Gender male	72 (36.7 %)	180 (32.4 %)	0.859
female	124 (63.3 %)	375 (67.6 %)	
ASA-score 1	27/196 (13.8 %)	51/555 (9.2 %	0.399
2	142/196 (72.4 %)	419/555 (75.5 %)	
3	27/196 (13.8 %)	77/555 (13.9 %)	
4	0 %	8/555 (1.4 %)	
Smoking	27/196 (13.8 %)	71/555 (12.8 %)	0.725
Nickel allergy	14/196 (7.1 %)	7/555 (1.3 %)	<0.001**
Deceased/lost to follow-up	4	25	0.124
Death after revision (days)	472 (±233)	344 (±206)	0.312
Operation Time (min)	102 (80,137)	99 (78; 127)	0.134
Serum Cell-count 10^9/l	8.5 (±5.1)	8.1 (±4.6)	0.917
Serum CRP (mg/l)	14.6 (±23.8)	9.7 (±14.4)	0.687
Hemoglobin (g/dl)	13.1 (±1.4)	13.4 (±1.5)	0.221
Preoperative aspiration	18 (9.2 %)	21 (3.8 %)	0.003*
Synovial cell-count (x10^9)	1.5 (±2.1)	1.2 (±1.1)	0.318
Synovial PMN (%)	45.4 % (±22.2)	30.4 (±15.5)	0.137
Synovial CRP (mg/l)	1.8 (±2.5)	0.45 (±0.35)	0.518
Re-revision	**41/196 (20.9 %)**	**67/555 (12.1 %)**	0.002*
Septic revisions after	12/196 (6.1 %)	10/555 (1.8 %)	0.002*
Single stage exchange	3/24 (12.5 %)	0/76 (0.0 %)	0.013*
Cup exchange	4/84 (4.8 %)	7/243 (2.9 %)	0.482
Stem exchange	4/41 (9.8 %)	0/102 (0.8 %)	0.006*
Modular exchange	0/32 (0.0 %)	1/93 (1.1 %)	>0.99
ORIF	1/12 (8.3 %)	1/32 (3.1 %)	0.476
Ossification	0/2 (0.0 %)	1/9 (11.1 %)	>0.99
Early septic revision ≤90 days	7/13 (53.8 %)	4/10 (40 %)	0.670
Late septic revision >90 days	5/13 (46.2 %)	6/10 (60 %)	0.670
Reason for aseptic re-revision	**29 (14.8 %)**	**57 (10.1 %)**	**0.091**
Aseptic loosening	3/29 (10.3 %)	29/57 (50.0 %)	<0.001**
Dislocation	16/29 (55.2 %)	16/57 (28.6 %)	0.020*
Wear	3/29 (10.3 %)	3/57 (5.4 %)	0.406
Fracture	4/29 (13.8 %)	6/57(10.8 %)	0.729
Other	3/29 (10.3 %)	3/57 (5.4 %)	0.406

5. UPICs in revision total knee arthroplasty

A total of 679 presumed aseptic rTHA were evaluated. There were 113/679 (16.6 %) UPICs and 566/679 (7383.4 %) CN results. UPIC revisions showed a significant higher rate of successful taps preoperatively compared to CN revisions (p < 0.001). The septic re-revision rate is higher in UPIC compared to CN results (p = 0.013). There is no significant higher aseptic re-revision rate between UPICs compared to CN results (p = 0.619). Nevertheless, the risk of a re-revision is threefold

Table 4
Baseline demographic, and operative data for revision total knee arthroplasty. Mean with SD (standard deviation), median with IQR (Interquartile-range); UPIC (unexpected positive intraoperative cultures) included presumed aseptic and inconclusive revisions; BMI (Body-Mass-Index); ASA (American Society of Anesthesiologists Classification); CRP (C-reactive protein); PMN (Polymorphonuclear neutrophils); ORIF (open reduction and internal fixation) The number of septic re-revisions after a specific operation is compared with the total number of this procedure; *<0.05; **<0.001.

Baseline demographic, and operative data for revision total knee arthroplasty			
Revision total knee arthroplasty	UPIC n = 113 (16.6 %)	CN n = 566 (72.6 %)	P-value
BMI	30.4 (±6.1)	30.4 (±5.8)	0.095
Age	70 (61; 77))	71 (64; 76)	0.607
Gender male	32 (28.3 %)	165 (27.6 %)	0.273
female	81 (71.7 %)	401 (72.4 %)	
ASA-score 1	12/113 (10.6 %)	58/566 (10.2 %)	0.892
2	89/113 (78.8 %)	449/566 (79.3)	
3	9/113 (7.9 %)	59/566 (10.4 %)	
4	3/113 (2.7 %)	0 %	
Smoking	18/113 (15.9 %)	61/566 (10.8 %)	0.119
Nickel allergy	8/113 (7.1 %)	10/566 (1.8 %)	0.005*
Deceased/lost to follow-up	3	14	>0.99
Death after revision (days)	506 (±191)	428 (±242)	0.614
Operation time (min)	125 (102; 146)	119 (93; 142)	0.106
Serum Cell-count 10^9/l	7.6 (±3.1)	7.5 (±2.3)	0.251
Serum CRP (mg/l)	5.0 (±4.7)	5.8 (±7.4)	0.561
Hemoglobin (g/dl)	13.9 (±1.3)	13.7 (±1.4)	0.431
Preoperative aspiration	46 (40.7 %)	62 (11.0 %)	<0.001**
Synovial cell-count (10^9)	1.0 (+0.9)	1.0 (±1.4)	0.618
Synovial PMN (%)	35.3 % (±12.3)	39.9 (±15.5)	0.190
Synovial CRP (mg/l)	1.3 (±1.3)	1.5 (±1.2)	0.430
Re-revision	**18/113 (15.9 %)**	**57/566 (10.1 %)**	0.098
Septic revision after	7/113 (6.2 %)	10/566 (1.8 %)	0.013*
Single stage exchange	4/87 (4.6 %)	6/389 (1.5 %)	0.024*
Inlay exchange	2/13 (15.4 %)	3/65 (4.6 %)	0.192
Patella resurfacing	0/9 (0.0 %)	1/94 (1.1 %)	>0.99
ORIF	1/2 (50.0 %)	0/7 (0.0 %)	0.222
Extensor tendon rupture	0/2 (0.0 %)	0/10 (0.0 %)	—
Early septic revision ≤90 days	1/7 (14.3 %)	2/10 (20 %)	>0.99
Late septic revision >90 days	6/7 (85.7 %)	8/10 (80 %)	
Reason for aseptic re-revision	11/113 (9.7 %)	47/566 (8.3 %)	0.619
Instability	1/11 (9.1 %)	23/47 (48.9 %)	0.013*
Aseptic loosening	3/11(27.3 %)	10/47 (21.3 %)	0.696
Wear	2/11(18.2 %)	2/47 (4.3 %)	0.159
Patella resurfacing	—	9/47 (19.1 %)	—
Quadriceps tendon rupture	2/11 (18.2 %)	—	—
Other	3/11 (27.3 %)	3/47 (6.4 %)	0.075

higher in UPICs compared to CN result. System exchange has a higher rate of septic-re-revision after UPIC rTHA compared to other reasons for revision. All results between UPIC and CN results in rTHA can be found in Table 3.

The area under the curve (AUC) for the time between primary/previous surgery and UPIC rTKA with septic revision as state variable was 0.792 (CI-95 % 0.555-1.00). Cut-off values based on Youdon-index were 539 days. Indicating revisions within 539 days after index surgery have a higher risk for septic re-revision than aseptic re-revisions in TKA. All patella resurfacing procedures were excluded from the calculation of operative time, as there was a significantly higher number in the CN group compared to the UPIC group, all other procedures were included in the calculation.

6. Discussion

In this currently largest study on UPIC's in presumed aseptic or ICM-inconclusive hip and knee revision arthroplasties, we found that the rate of UPIC was generally higher in the hip than in the knee. UPIC results had a higher septic and aseptic re-revision rate compared to CN results. Risk factors for septic failure in this study were, conversion revisions, single-stage-exchange revisions and early revision after index surgery. In addition, nickel allergy was a risk factor for having an UPIC.

The UPIC rate in this study was higher than in other studies, especially in rTHA [5,6,24,25]. However, other studies included only unexpected positive cases. Our study, included both clear UPICs and inconclusive patients according to the ICM-2018 criteria. The higher rate of UPICs in rTHA compared to rTKA may be explained by the higher rate of single-stage exchanges and the lower rate of single-component exchanges in rTKA compared to rTHA. Another reason could be the significantly lower preoperative diagnostic workup for PJI and the presence of inconclusive revisions according to ICM-2018 criteria. In the study by *Jacobs* et al. rTHA also had a higher rate of UPIC compared to rTKA [12]. Therefore, all patients with presumed aseptic revision arthroplasty should undergo a thorough diagnostic workup and if infection is still suspected, intraoperative cultures should be obtained during surgery in order to select the appropriate treatment [5,9,13].

Overall, the infection-free implant survival in this study is comparable to that reported by *Neufeld* et al. who reported infection-free implant survival in UPIC rTHA and rTKA of 86 % and 95 %, respectively, at 5 years [8,25]. Interestingly, not only are septic re-revisions higher, but also aseptic re-revisions are significantly higher in UPIC revisions compared to CN revisions. In addition, if the same microorganism was found in the UPIC revision and the septic re-revision, then all microorganisms have gained resistance to antibiotics. In the study by *Frank* et al. and *Mitterer* et al. changes in the microbiological spectrum and resistance pattern are common between different septic revisions [23,26]. The question remains whether these aseptic re-revisions are truly aseptic or undiagnosed chronic PJI. Therefore, septic failure due to CN PJI may be higher than expected. These patients are known to have poor outcomes and a high rate of salvage procedures [27].

The risk of re-revision in THAs with two or more cultures of the same bacteria was not increased in the paper by *Milandt* et al [16]. In this study, high virulent microorganisms, a previous septic revision, UPICs with ≥2 culture-positive specimens and inconclusive revisions according to ICM-2018 criteria, did not show a higher septic or aseptic failure rate. One explanation may be that these patients were significantly more likely to be treated with appropriate antibiotics for several weeks, depending on resistance.

The time period for septic failure after UPIC is shorter than the time period for aseptic failure. The time period in this study is a common time period for PJI revision [28]. Early revisions with UPIC should probably be treated as infected due to a higher septic re-revision rate.

In addition, patients with nickel allergy showed a higher risk for UPICs in both rTHA and rTKA. The study by *Neufeld* et al. reported adverse metal reaction as a risk factor for subsequent PJI in patients with UPC [8]. The study by *Prieto* et al. reported high rates of infection after aseptic revision due to adverse metal reaction because of a change in the local environment that predisposing to infection [29]. The higher rate of UPIC in nickel allergy patients in this study may be partially explained by adverse tissue reactions as described by *Kirchen* et al [30]. However, in the Australian registry study by *Vertullo* et al. an allergy friendly TKA did not reduce revision rates for PJI or loosening [31]. Nickel allergy patients in this study also did not show a higher rate of septic re-revision, which can probably be interpreted as contamination, especially with low virulence microorganisms.

The present study has several limitations. First, the retrospective nature of the study design, with all its disadvantages. Second, due to the incomplete preoperative workup, occult infection could not always be ruled out. Third, the preoperative evaluation and clinical routine for the

treatment of UPIC in rTKA and rTHA have changed over time. Moreover, different surgeons with different experience preformed surgical procedures. Nevertheless, these are real-world data.

In conclusion, UPICs have a higher rate of septic and aseptic failure than CN outcomes. UPICs are twice as common in rTHA compared to rTKA. Preoperative PJI workup reduces the UPIC rate. Nickel allergy is a risk factor for UPIC, but did not show a higher rate of septic re-revision. Early revisions with UPICs after primary THA or TKA have a higher risk septic failure. UPICs with high virulent microorganisms, a previous septic revision, UPICs with $\geq$2 culture-positive specimens and inconclusive ICM-2018 criteria should be treated with ABs.

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Declaration of Competing Interest

None.

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References

[1] Heckmann ND, Yang J, Ong KL, Lau EC, Fuller BC, Bohl DD, et al. Revision surgery for instability after total hip arthroplasty: does timing matter? J Arthroplasty 2021; 36:1779–1783.e2. https://doi.org/10.1016/j.arth.2020.12.035.
[2] Lewis PL, Robertsson O, Graves SE, Paxton EW, Prentice HA, W-Dahl A. Variation and trends in reasons for knee replacement revision: a multi-registry study of revision burden. Acta Orthop 2021;92:182–8. https://doi.org/10.1080/17453674.2020.1853340.
[3] Kingsbury SR, Smith LK, Shuweihdi F, West R, Czoski Murray C, Conaghan PG, et al. A comparative study of patients presenting for planned and unplanned revision hip or knee arthroplasty. Bone Joint Lett J 2022;104-B:59–67. https://doi.org/10.1302/0301-620X.104B1.BJJ-2021-0032.R2.
[4] Hipfl C, Mooij W, Perka C, Hardt S, Wassilew GI. Unexpected low-grade infections in revision hip arthroplasty for aseptic loosening. Bone Joint Lett J 2021;103-B: 1070–7. https://doi.org/10.1302/0301-620X.103B6.BJJ-2020-2002.R1.
[5] Purudappa PP, Sharma OP, Priyavadana S, Sambandam S, Villafuerte JA. Unexpected positive intraoperative cultures (UPIC) in revision Hip and knee arthroplasty- A review of the literature. J Orthop 2020;17:1–6. https://doi.org/10.1016/j.jor.2019.06.028.
[6] Ribera A, Morata L, Moranas J, Agulló JL, Martínez JC, López Y, et al. Clinical and microbiological findings in prosthetic joint replacement due to aseptic loosening. J Infect 2014;69:235–43. https://doi.org/10.1016/j.jinf.2014.05.003.
[7] Barrack RL, Aggarwal A, Burnett RSJ, Clohisy JC, Ghanem E, Sharkey P, et al. The fate of the unexpected positive intraoperative cultures after revision total knee arthroplasty. J Arthroplasty 2007;22:94–9. https://doi.org/10.1016/j.arth.2007.03.029.
[8] Neufeld ME, Lanting BA, Shehata M, Howard JL, MacDonald SJ, Teeter MG, et al. Prevalence and outcomes of unexpected positive intraoperative cultures in presumed aseptic revision hip arthroplasty. J bone jt surg. Publish Ah; 2021. https://doi.org/10.2106/JBJS.20.01559.
[9] Saleh A, Guirguis A, Klika AK, Johnson L, Higuera CA, Barsoum WK. Unexpected positive intraoperative cultures in aseptic revision arthroplasty. J Arthroplasty 2014;29:2181–6. https://doi.org/10.1016/j.arth.2014.07.010.
[10] Bereza PL, Ekiel A, Auguściak-Duma A, Aptekorz M, Wilk I, Wojciechowski P, et al. Identification of asymptomatic prosthetic joint infection: microbiologic and operative treatment outcomes. Surg Infect 2017;18:582–7. https://doi.org/10.1089/sur.2016.253.
[11] Simon S, Frank BJH, Aichmair A, Dominkus M, Mitterer JA, Hartmann SG, et al. Alpha-defensin as a diagnostic tool in revision total knee arthroplasties with unexpected positive intraoperative cultures and unexpected culture negative intraoperative cultures. Knee Surgery, Sport Traumatol Arthrosc 2023;31:1462–9. https://doi.org/10.1007/s00167-022-07268-w.
[12] Jacobs AME, Bénard M, Meis JF, van Hellemondt G, Goosen JHM. The unsuspected prosthetic joint infection. Bone Joint Lett J 2017;99-B:1482–9. https://doi.org/10.1302/0301-620X.99B11.BJJ-2016-0655.R2.
[13] Kloos J, Vander Linden K, Vermote S, Berger P, Vandenneucker H. Prevalence, interpretation, and management of unexpected positive cultures in revision TKA: a systematic review. Knee Surgery 2022. https://doi.org/10.1007/s00167-021-06856-6. Sport Traumatol Arthrosc.
[14] Portillo ME, Salvadó M, Alier A, Sorli L, Martínez S, Horcajada JP, et al. Prosthesis failure within 2 Years of implantation is highly predictive of infection. Clin Orthop Relat Res 2013;471:3672–8. https://doi.org/10.1007/s11999-013-3200-7.
[15] Boot W, Moojen DJF, Visser E, Lehr AM, De Windt TS, Van Hellemondt G, et al. Missed low-grade infection in suspected aseptic loosening has no consequences for the survival of total hip arthroplasty. Acta Orthop 2015;86:678–83. https://doi.org/10.3109/17453674.2015.1086942.
[16] Milandt NR, Gundtoft PH, Overgaard S. A single positive tissue culture increases the risk of rerevision of clinically aseptic THA: a national register study. Clin Orthop Relat Res 2019;477:1372–81. https://doi.org/10.1097/CORR.0000000000000609.
[17] Vargas-Reverón C, Soriano A, Fernández-Valencia JA, Martínez-Pastor JC, Morata L, Muñoz-Mahamud E. Prevalence and impact of positive intraoperative cultures in partial hip or knee revision. J Arthroplasty 2020;35:1912–6. https://doi.org/10.1016/j.arth.2020.02.025.
[18] Staats K, Kolbitsch P, Sigmund IK, Hobusch GM, Holinka J, Windhager R. Outcome of total hip and total knee revision arthroplasty with minor infection criteria: a retrospective matched-pair analysis. J Arthroplasty 2017;32:1266–71. https://doi.org/10.1016/j.arth.2016.11.016.
[19] Pérez-Prieto D, Hinarejos P, Alier A, Sorlí L, Martínez S, Puig L, et al. Adherence to a reliable PJI diagnostic protocol minimizes unsuspected positive cultures rate. BMC Musculoskelet Disord 2021;22:653. https://doi.org/10.1186/s12891-021-04431-1.
[20] Antonios JK, Lim ES, Chang Y-HH, Bingham JS, Clarke HD, Spangehl MJ, et al. The fate of the inconclusive periprosthetic joint infection workup and reliability of data points. Orthopedics 2023;46. https://doi.org/10.3928/01477447-20230310-08.
[21] van Sloten M, Gómez-Junyent J, Ferry T, Rossi N, Petersdorf S, Lange J, et al. Should all patients with a culture-negative periprosthetic joint infection be treated with antibiotics? Bone Joint Lett J 2022;104-B:183–8. https://doi.org/10.1302/0301-620X.104B1.BJJ-2021-0693.R2.
[22] Parvizi J, Tan TL, Goswami K, Higuera C, Della Valle C, Chen AF, et al. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. J Arthroplasty 2018;33:1309–1314.e2. https://doi.org/10.1016/j.arth.2018.02.078.
[23] Frank BJH, Aichmair A, Simon S, Schwarz GM, Dominkus M, Hofstaetter JG. Analysis of culture positive first and second stage procedures in periprosthetic knee and hip joint infections. J Arthroplasty 2021. https://doi.org/10.1016/j.arth.2021.01.074.
[24] Neufeld ME, Lanting BA, Shehata M, Howard JL, MacDonald SJ, Teeter MG, et al. Prevalence and outcomes of unexpected positive intraoperative cultures in presumed aseptic revision hip arthroplasty. J Bone Jt Surg 2021;103:1392–401. https://doi.org/10.2106/JBJS.20.01559.
[25] Neufeld ME, Lanting BA, Shehata M, Naudie DDR, McCalden RW, Teeter MG, et al. The prevalence and outcomes of unexpected positive intraoperative cultures in presumed aseptic revision knee arthroplasty. J Arthroplasty 2022;37:2262–71. https://doi.org/10.1016/j.arth.2022.05.036.
[26] Mitterer JA, Frank BJH, Gardete-Hartmann S, Panzenboeck LF, Simon S, Krepler P, et al. Changes of the microbiological spectrum and antibiotic resistance pattern in postoperative spinal implant infections with multiple culture-positive revision surgeries. Spine J 2022;22:1934–43. https://doi.org/10.1016/j.spinee.2022.07.086.
[27] Tan TL, Kheir MM, Shohat N, Tan DD, Kheir M, Chen C, et al. Culture-negative periprosthetic joint infection. JBJS Open Access 2018;3:e0060. https://doi.org/10.2106/JBJS.OA.17.00060.
[28] Gundtoft PH, Overgaard S, Schønheyder HC, Møller JK, Kjærsgaard-Andersen P, Pedersen AB. The "true" incidence of surgically treated deep prosthetic joint infection after 32,896 primary total hip arthroplasties. Acta Orthop 2015;86: 326–34. https://doi.org/10.3109/17453674.2015.1011983.
[29] Prieto HA, Berbari EF, Sierra RJ. Acute delayed infection: increased risk in failed metal on metal total hip arthroplasty. J Arthroplasty 2014;29:1808–12. https://doi.org/10.1016/j.arth.2014.04.008.
[30] Kirchen N, Reich L, Waldstein W, Hopf T, Heller K-D, Wienert S, et al. ARMD-Reaktionsmuster bei Kniegelenkendoprothesen. Orthopä 2020;49:183–9. https://doi.org/10.1007/s00132-019-03776-9.
[31] Vertullo Christopher J, Lewis Peter L, Graves Stephen, Kelly Lan, Michelle Lorimer PM. Twelve-year outcomes of an oxinium total knee replacement compared with the same cobalt-chromium design: an analysis of 17,577 prostheses from the Australian orthopaedic association national joint replacement registry. J Bone Jt Surg 2017;99:e37. https://doi.org/10.2106/JBJS.ER.16.00092.