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Complications - Infection

The Prevalence and Outcomes of Unexpected Positive Intraoperative Cultures in Presumed Aseptic Revision Knee Arthroplasty

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ABSTRACT

Background: The prevalence and outcomes of unexpected positive intraoperative cultures (UPC) in presumed aseptic revision total knee arthroplasty (TKA) are unclear. The purpose of this study was to determine the prevalence of UPC and infection-free implant survival in this patient population. Secondly, we aimed to compare the infection-free implant survival between cohorts based on number of UPCs and antibiotic treatment.
Methods: We reviewed our institutional database from 2006 to 2019 for all TKA revisions (n = 1795) to identify all presumed aseptic TKA revisions with intraoperative culture(s). After exclusions, 775 revisions were eligible and those with UPC were included in the Kaplan-Meier analysis to determine infection-free implant survival for the cohorts.
Results: The prevalence of UPC was 9.8%. The 2- and 5-year infection-free survival was 97.4% and 95.3%, respectively. The 5-year infection-free survival from the same microorganism as the UPC was 98.7%. Infection-free survival was similar for the 1 versus ≥2 UPC cohorts ($P = .416$), however was poorer for the cohort treated with antibiotics ($P = .021$). Only one of 3 subsequent PJI-related implant failures was caused by the same microorganism (polymicrobial) as the UPC. There were no subsequent infections in patients with a single UPC not treated with antibiotics.
Conclusions: The prevalence of UPC was 9.8% and the infection-free implant survival is excellent. Infection-free survivorship from PJI caused by the same UPC microorganism is outstanding. Comparisons between cohorts must be interpreted with caution due to study limitations. A single UPC in patents without other signs of infection does not require antibiotic treatment.
Level of Evidence: IV.

Currently over 1 million total knee arthroplasty (TKA) are performed in North America annually [1,2], and this will increase markedly [1,3]. At the 10-year mark, up to 12% of primary TKA require revision surgery [4], and the number of revisions is also projected to increase substantially [3]. Periprosthetic joint infection (PJI) is a leading cause for revision, is associated with enormous cost and morbidity, and rates are not declining [5–8]. Despite the immense scientific effort there remains no perfect test to diagnose PJI in TKA [9–11], and a proportion of presumed aseptic failures may be unrecognized PJI [12–14]. Thus, unexpected positive intraoperative cultures (UPC) in presumed aseptic revisions do occur and can be expected to remain a problem. UPCs

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Table 1
Baseline, Demographic, and Operative Data of Study Population of 76 UPC Revisions.

Variable	
Age (y)[a]	69.3 (9.0)
Sex, F/M, n (%)	47/29 (61.8/38.2)
BMI (kg/m^2)[b]	33.6 (28.6 to 37.8)
ASA classification, n (%)	
1	0 (0)
2	18 (23.7)
3	56 (73.7)
4	2 (2.6)
Smoking, n (%)	10 (13.2)
Diabetes, n (%)	18 (23.7)
Anticoagulation, n (%)	7 (9.2)
Inflammatory condition, n (%)	10 (13.2)
Etiology for primary TKA, n (%)	
Osteoarthritis	66 (86.8)
Rheumatoid/inflammatory arthritis	5 (6.6)
Avascular necrosis/SONK	2 (2.6)
Post-traumatic arthritis	2 (2.6)
Other	1 (1.3)
Reasons for revision, n (%)	
Aseptic loosening	34 (44.7)
Instability	22 (28.9)
Arthrofibrosis	6 (7.9)
Polyethylene wear ± osteolysis	4 (5.3)
Patellar problem	4 (5.3)
Pain no known source	4 (5.3)
Periprosthetic fracture	1 (1.3)
Pain component malposition	1 (1.3)
Revision number[b]	1.0 (1.0 to 1.0)
History of prior TKA revision in study joint, n (%)	11 (14.5)
Age of prosthesis (y)[b]	8.9 (3.3 to 14.6)
History of PJI in study joint, n (%)	2 (2.6)
Preoperative serum CRP >10 mg/L, n (%)	9 (11.8)
Missing data CRP, n (%)	1 (1.3)
Preoperative serum ESR >30mm/h n (%)	7 (9.2)
Missing data ESR, n (%)	1 (1.3)
Preoperative joint aspirate, n (%)	24 (31.6)
Type of revision, n (%)	
Patella	4 (5.3)
Modular exchange	8 (10.5)
1-component	8 (10.5)
2-component	56 (73.7)
Antibiotic cement used, n (%)	70 (92.1)
Cemented stems used, n (%)	9 (11.8)

UPC, unexpected positive intraoperative culture; F, female; M, male; BMI, body mass index; ASA, American society of anesthesiologists; TKA, total knee arthroplasty; SONK, spontaneous osteonecrosis of the knee; PJI, periprosthetic joint infection; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate.
[a] Values are mean (standard deviation).
[b] Values are median (interquartile range).

Table 2
Sampling, Microorganism, Treatment, and Outcome Data for Study Population of 76 UPC Revisions.

Variable	
Number of samples taken in study revision[a]	4 (3.0 to 5.0)
Total samples taken, n	295
Swab samples, n (%)	113 (38.3)
Fluid samples, n (%)	20 (6.8)
Tissue samples, n (%)	162 (54.9)
Total number of UPC's, n	93
UPC broth, n (%)	48 (51.6)
UPC solid, n (%)	45 (48.4)
1 UPC versus ≥ 2 UPC, n (%)	
1 UPC	62 (81.6)
≥2 UPC	14 (18.4)
Microorganisms, n (%)[b]	
C. acnes	33 (32.4)
Other CNS	23 (22.5)
MSSE	22 (21.6)
MRSE	1 (1.0)
Streptococcus sp	8 (7.8)
Enterococcus sp	4 (3.9)
Bacillus sp.	3 (2.9)
Corynebacterium sp	2 (2.0)
Others (6 species)	6 (5.9)
Number of revisions resistant UPC, n (%)	4 (5.3)
Number revisions polymicrobial UPC, n (%)	12 (15.8)
Surgical treatment of UPC, n (%)	1 (1.3)
Antibiotic treatment of UPC, n (%)	27 (35.5)
Antibiotic route, n (%)	
Oral alone	12 (44.4)
IV alone	9 (33.3)
Combined IV and oral	6 (22.2)
Antibiotic duration, n (%)	
≤6 wk	25 (92.6)
≤3 mo	1 (3.7)
≤6 mo	1 (3.7)
Subsequent aseptic revision, n (%)[c]	4 (5.3)
Etiology subsequent aseptic revision, n (%)	
Instability	1 (25.0)
Aseptic loosening	1 (25.0)
Periprosthetic fracture	1 (25.0)
Avascular necrosis patella	1 (25.0)
Time to subsequent aseptic revision (y)[d]	3.5 (2.7)
Subsequent PJI, n (%)	3 (3.9)
Subsequent PJI microorganism, n (%)	
Same as UPC microorganism	0 (0)
Mixed	1 (33.3)
Different than UPC microorganism	2 (66.7)

UPC, unexpected positive intraoperative culture; *C. acnes*, *Cutibacterium acnes*; CNS, coagulase-negative *Staphylococcus* species; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; sp, species; IV, intravenous; PJI, periprosthetic joint infection.
[a] Values are median (interquartile ranges).
[b] Reported as microorganism(s) grown from each intraoperative specimen that was positive (UPC).
[c] Subsequent aseptic revision after the study revision, censored out of survival analysis once occurs as subsequent PJI could be caused by subsequent aseptic revision.
[d] Values are mean (standard deviation).

are clinically challenging because the surgeon becomes aware of the UPC after the presumed aseptic revision surgery, and the surgical management of aseptic versus infection-related failure differs substantially.

The prevalence of UPC in presumed aseptic revision TKA remains unclear (4%-38%), as does the optimal treatment and the clinical consequences in terms of infection-free survival [12,15–19]. The clinical significance of PJI diagnosed by UPC remains controversial, and the significance of a single UPC in presumed aseptic revision is even more uncertain [15–17,19,20]. The literature on UPC in revision TKA is inadequate and larger studies are needed [19].

Our primary aim was to determine the prevalence of UPC in presumed aseptic revision TKA and the infection-free implant survival for this cohort. Secondarily, we aimed to compare the infection-free implant survival between patients with (I) 1 versus ≥2 UPCs and, (II) UPC(s) treated with antibiotics versus those presumed to be a contaminant and not treated with antibiotics.

Patients and Methods

Our prospectively maintained institutional database was used to identify all 1,795 revision TKA cases performed at our academic tertiary care center between January 2006 and April 2019. A retrospective review of operative notes and electronic medical records was performed to apply study inclusion and exclusion criteria. Patients that underwent presumed aseptic single-stage revision TKA with intraoperative culture samples(s) taken were eligible for inclusion. Revisions with no intraoperative samples taken for culture were excluded, as were revisions of patellofemoral or unicompartmental replacements. Patients on chronic antibiotic suppression for PJI were excluded. Revisions were excluded if PJI was

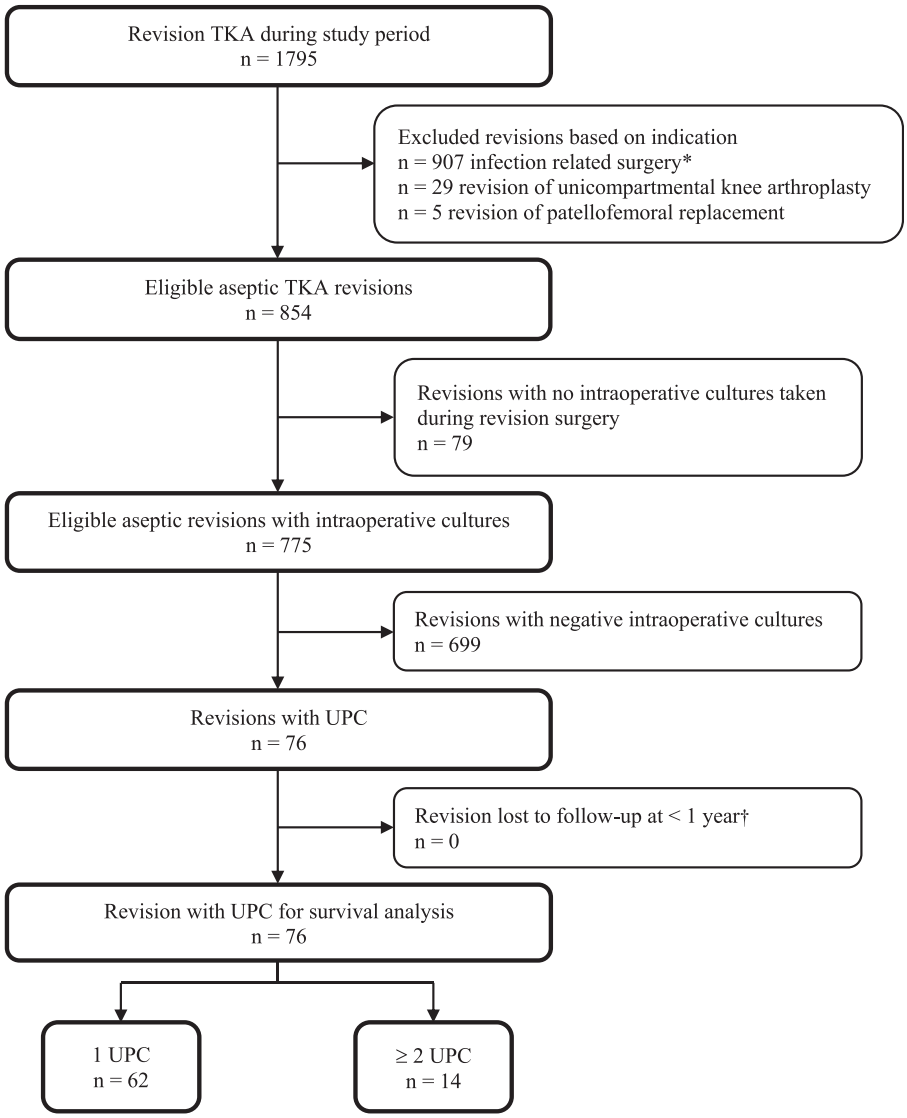

Fig. 1. Flowchart of eligible aseptic total knee arthroplasty (TKA) revisions and revisions with unexpected positive intraoperative cultures (UPC). *Infection related surgeries include 1-stage, 2-stage, and debridement, antibiotics, and implant retention with modular exchange for periprosthetic joint infection, as well as revisions with known suppressed infection or those suspected of being infected. †Revisions that had the endpoint of subsequent infection-related implant failure, or those that had subsequent aseptic revision surgery prior to 1-year follow-up were not excluded from survival analysis.

known or suspected preoperatively, or were part of the treatment for PJI (debridement, antibiotics with retention of nonmodular implants, 1-stage or 2-stage revision for PJI). Patients lost to follow-up less than 1-year from the index study revision were excluded, unless this was secondary to a subsequent aseptic revision (censored in survival analysis) or recurrent PJI (study end-point). The base cohort to determine the prevalence of UPC was comprised of revisions meeting inclusion/exclusion criteria, and of these, the final UPC study cohort was comprised of revisions with a minimum of 1 UPC (organism in broth or sold medium). Ethics approval was obtained from our institutional research ethics board.

For the UPC study cohort a manual review of electronic medical records was performed to obtain patient, demographic, laboratory, microbiological, surgical, treatment, and outcome data (Tables 1 and 2). All revisions were evaluated preoperatively for PJI both clinically and with serum C-reactive protein and erythrocyte sedimentation rate, only obtaining a joint fluid aspirate if any of these parameters were suspicious for PJI. The number and type (swab, fluid aspirate, tissue) of intraoperative samples taken for culture was not standardized and was dependent on the preference of the treating surgeon (9 surgeons). For each UPC, the microorganism, antibiotic sensitivities, and broth or solid medium status was documented. Each individual intraoperative sample sent for culture that had growth of a microorganism(s) was considered a single UPC. All cement in revisions contained antibiotics (Bone Cement Antibiotic Simplex P with Tobramycin 1g; Stryker, Kalamazoo, MI). All patients received postoperative antibiotic prophylaxis (Ancef unless patient allergy). The duration of postoperative prophylactic antibiotics varied (1-5 days) based solely on the differing routine revision prophylactic preferences of the treating surgeons.

Antibiotic treatment of UPC(s) was defined as the administration of microorganism-specific antibiotics for the purpose of treating an UPC after the UPC was discovered. Postoperative

Table 3
Patient, Operative, Microorganism, and Treatment Data for Revisions With an UPC that had a Subsequent PJI-Related Implant Failure.

Variable	Case 1	Case 2	Case 3
Age (y)	73	68	90
Sex	Female	Female	Male
BMI (kg/m^2)	30.7	55.8	27.1
Etiology for primary TKA	Osteoarthritis	Osteoarthritis	Osteoarthritis
Revision number	1	1	1
Age of prosthesis (y)	8	17	4
Reason for revision	Aseptic loosening	Aseptic loosening	Instability
History of PJI in study joint	No	No	No
Preoperative serum CRP (mg/L)	0.3	8.5	1.2
Preoperative serum ESR (mm/h)	9	13	7
Preoperative joint aspirate	No	Yes	No
Type of revision	2-component	2-component	Modular exchange
Number of UPC's	1	1	1
UPC solid or broth	Solid	Broth	Broth
UPC microorganism(s)	*C. acnes*	*Staph warneri*	MRSE
Surgical treatment UPC	No	No	No
Antibiotic treatment UPC	6 wk oral	6 wk oral	6 wk oral
Time to subsequent PJI (y)	0.2	0.3	2.7
Microorganism(s) subsequent PJI	*C. acnes* + *Proteus Mirabilis*	MSSA	Culture-negative

UPC, unexpected positive intraoperative culture; PJI, periprosthetic joint infection; BMI, body mass index; TKA, total knee arthroplasty; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; *C. acnes, Cutibacterium acnes*; *Staph*, *Staphylococcus*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; MSSA, methicillin-sensitive *Staphylococcus aureus.*

antibiotic prophylaxis was not considered as UPC antibiotic treatment. There was neither a predefined treatment protocol for UPC at our institution, nor routine interdisciplinary rounds. UPC treatment decisions were made on a case-by-case basis with the surgeon and an infectious disease specialist based on a combination of patient, surgical, and microbiologic factors.

Infection-related implant failure was defined as the occurrence of infection that required antibiotic treatment or revision surgery for PJI at any time after the index study revision. Since the year 2012, the diagnosis of PJI at our institution was made according to the Musculoskeletal Infection Society definition for PJI criteria and updated versions [9,10]. The causative microorganism(s) of any subsequent PJI-related failure was recorded and compared to the microorganism(s) of the index revision surgery UPC. All subsequent PJI was treated with surgery and antibiotics. If a subsequent aseptic revision occurred it was documented, as well as the etiology and time from index study revision. Latest EMR clinical follow-up was used as latest follow-up, unless subsequent PJI, subsequent aseptic revision, or death occurred first (in order of occurrence).

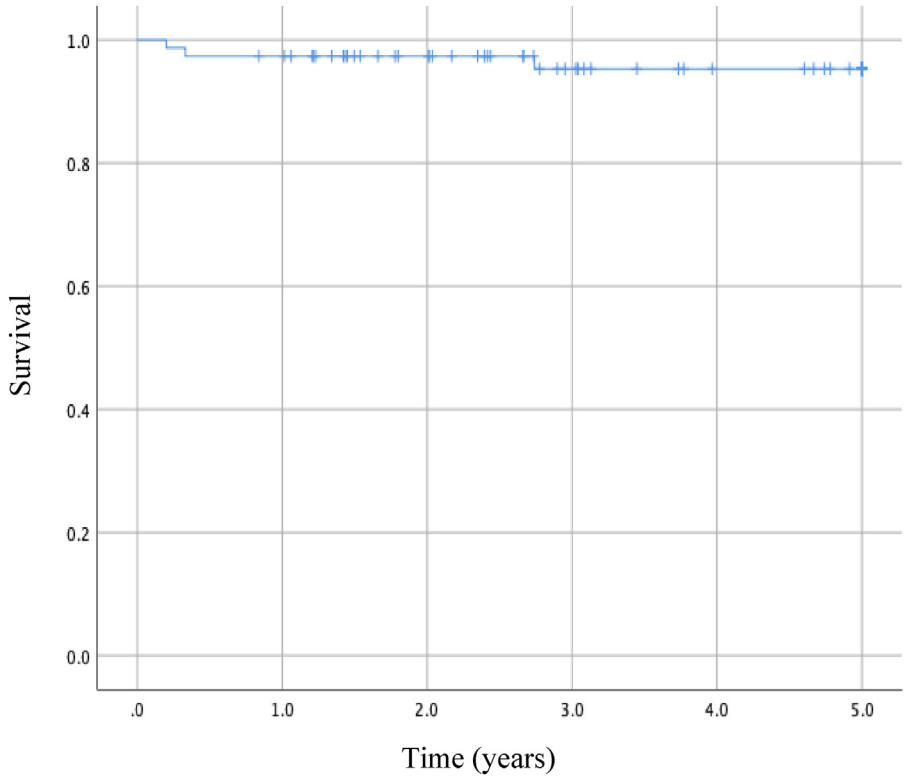

Fig. 2. Kaplan-Meier 5-year infection-free survival for entire unexpected positive intraoperative culture cohort in presumed aseptic knee revisions. Vertical spikes are censored data.

Secondary study aims were accomplished by creating cohorts from the UPC study cohort: (I) a 1 UPC versus ≥2 UPC cohort based on number of UPCs, and (II) an UPC treated with antibiotics cohort versus not treated with antibiotics cohort (considered contaminant).

Statistical Analysis

Statistical analysis was performed using the SPSS v26.0 (IBM Inc, Armonk, NY). Medians and interquartile ranges (IQR) or means and standard deviations (SD) were used, when appropriate. The Kaplan-Meier technique with 95% confidence intervals (CI) was used to determine the infection-free implant survival at 2 and 5-years for UPC study cohort, with subsequent PJI as the end-point. Patients who died, underwent subsequent aseptic revision, or were lost to follow-up after the 1-year mark were censored. The 5-year Kaplan-Meier survival was repeated for the entire UPC cohort using subsequent PJI caused by same microorganism as the UPC as the end-point. The 5-year infection-free survival was also calculated for all cohorts of interest. Log-rank tests were used to compare infection-free survival between cohorts. Continuous data was compared using Mann-Whitney *U* tests or 2-sample *t* tests for nonparametric and parametric data, respectively. The Shapiro–Wilk test was used to test normality. Categorical data was compared using the Pearson's chi-squared test or Fisher's exact test, when appropriate. Statistical significance was 2-tailed and set at a *P*-value ≤ .05.

Results

The base cohort was comprised of 775 single-stage presumed aseptic revisions with intraoperative cultures taken (Fig. 1). The prevalence of ≥1 UPC in presumed aseptic revision TKA was 9.8% (76/775). No revisions were lost to follow-up before 1-year for reasons other than subsequent aseptic revision or PJI. The median follow-up time was 3.6 years (IQR 2.0 to 6.2). Ten revisions with an UPC died at a mean of 5.3 years (SD 2.5), none before the 1-year mark.

Baseline and operative data for UPC cohort is shown in Table 1. Aseptic loosening and instability were the dominant modes of failure, preoperative serum C-reactive protein and erythrocyte sedimentation rate were elevated in 11.8% (9) and 9.2% (7) of revisions, and 31.6% (24) of revisions underwent a preoperative joint aspiration. The majority (73.7%) of patients underwent a 2-component revision. Microbiological, treatment, and outcome data analyzed (Table 2) show that 54.9% (162) of operative samples for culture were tissue and a median 4 samples (IQR 3 to 5) were taken per revision. Nearly 82% (62) of the cohort had a single UPC and 51.6% (48) of UPCs were grown in broth only. Coagulase-negative *Staphylococcus species* comprised 45.1% of all microorganisms, with 21.6% methicillin-sensitive *Staphylococcus epidermidis* and 23.5% other Coagulase-negative *Staphylococcus species* (Table 2). The most common microorganism grown in UPC was *Cutibacterium acnes (C. acnes)* (32.4%). Only 35.5% (27) of patients received antibiotic treatment for their UPC, the vast majority (92.6%) for duration of ≤6 weeks, though route of antibiotics varied (Table 2).

Three patients were diagnosed with a subsequent PJI at a mean of 1.1 years (SD 1.4) (Table 3). Of note, 2/3 of subsequent PJIs were caused by a different microorganism than the UPC, and 1/3 was polymicrobial with 1 causative microorganism the same as the UPC (Tables 2 and 3). The 2- and 5-year infection-free survival for the entire UPC cohort was 97.4% (95% CI 95.6% to 99.2%) and 95.3% (92.6% to 98.0%), respectively (Fig. 2). When considering only infection-related implant failure caused by the same microorganism as the UPC as the endpoint, the 5-year infection-free survival for the entire UPC cohort was 98.7% (95% CI 97.4% to 100%) (Fig. 3).

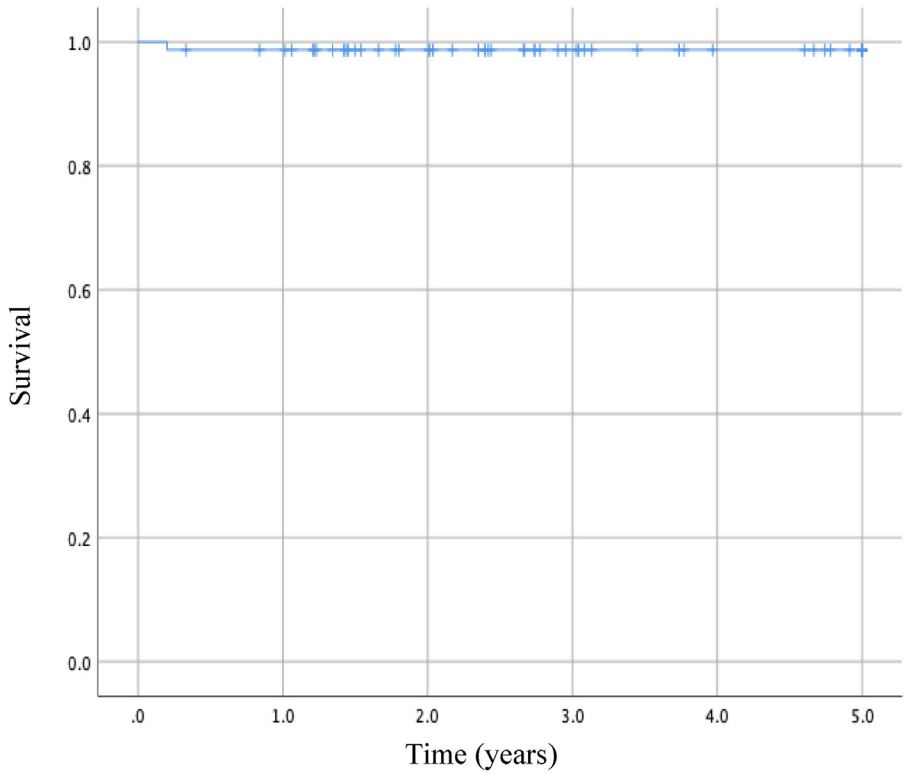

Fig. 3. Kaplan-Meier 5-year infection-free survival for entire unexpected positive intraoperative culture (UPC) cohort with subsequent periprosthetic joint infection by the same microorganism as the UPC as the endpoint. Vertical spikes are censored data.

Table 4
Baseline, Demographic, Operative, Microbiological, Treatment, and Outcome Data for Revisions With 1 UPC Versus ≥2 UPC.

Variable	1 UPC (n = 62)	≥2 UPC (n = 14)	*P* Value
Age (y)[a]	69.2 (8.8)	69.6 (9.8)	.872
Sex, F/M, n (%)	36/26 (58.1/41.9)	11/3 (78.6/21.4)	.154
BMI (kg/m^2)[b]	33.3 (28.5 to 38.0)	34.7 (31.3 to 38.2)	.445
ASA classification, n (%)			.294
1	0 (0)	0 (0)	
2	16 (25.8)	2 (14.3)	
3	45 (72.6)	11 (78.6)	
4	1 (1.6)	1 (7.1)	
Diabetes, n (%)	15 (24.2)	3 (21.4)	1.000
Inflammatory condition, n (%)	9 (14.5)	1 (7.1)	.678
Etiology for primary TKA, n (%)			.678
Osteoarthritis	53 (85.5)	13 (92.9)	
Other	9 (14.5)	1 (7.1)	
Reasons for revision, n (%)			.926
Aseptic loosening	29 (46.8)	5 (35.7)	
Instability	17 (27.4)	5 (35.7)	
Arthrofibrosis	5 (8.1)	1 (7.1)	
Polyethylene wear ± osteolysis	3 (4.8)	1 (7.1)	
Patellar problem	3 (4.8)	1 (7.1)	
Pain no known source	3 (4.8)	1 (7.1)	
Periprosthetic fracture	1 (1.6)	0 (0)	
Pain component malposition	1 (1.6)	0 (0)	
History of prior TKA revision in study joint n (%)	10 (16.1)	1 (7.1)	.678
Age of prosthesis (y)[b]	8.7 (3.1 to 13.9)	12.0 (5.5 to 16.3)	.366
History of PJI in study joint, n (%)	2 (3.2)	0 (0)	1.000
Pre-operative serum CRP >10 mg/L, n (%)	8 (12.9)	1 (7.1)	1.000
Pre-operative serum ESR >30 mm/h, n (%)	6 (9.7)	1 (7.1)	1.000
Preoperative joint aspirate, n (%)	20 (32.3)	4 (28.6)	1.000
Type of revision, n (%)			.391
Patella	2 (3.2)	2 (14.3)	
Modular exchange	7 (11.3)	1 (7.1)	
1-component	7 (11.3)	1 (7.1)	
2-component	46 (74.2)	10 (71.4)	
Number of samples taken in study revision[b]	4.0 (3.0 to 5.0)	4.0 (3.0 to 5.0)	.217
Swab used for culture in revision, n (%)	43 (69.4)	11 (78.6)	.745
Fluid used for culture in revision, n (%)	16 (25.8)	4 (28.6)	1.000
Tissue used for culture in revision, n (%)	50 (80.6)	9 (64.3)	.284
UPC broth or solid, n (%)			.379
Broth	30 (48.4)	18 (58.1)	
Solid	32 (51.6)	13 (41.9)	
Microorganisms, n (%)[c]			.029
C. acnes	24 (36.9)	9 (24.3)	
Other CNS	16 (24.6)	7 (18.9)	
MSSE	8 (12.3)	14 (37.8)	
MRSE	1 (1.5)	0 (0)	
Streptococcus sp	6 (9.2)	2 (5.4)	
Enterococcus sp	1 (1.5)	3 (8.1)	
Others	9 (13.8)	2 (5.4)	
Number of revisions resistant UPC, n (%)	2 (3.2)	2 (14.3)	.152
Antibiotic treatment of UPC, n (%)	18 (29.0)	9 (64.3)	.027
Antibiotic route, n (%)			.123
Oral alone	10 (55.6)	2 (22.2)	
IV alone	6 (33.3)	3 (33.3)	
Combined IV and oral	2 (11.1)	4 (44.4)	
Antibiotic duration, n (%)			.103
≤6 wk	18 (100.0)	7 (77.8)	
≤3 mo	0 (0)	1 (11.1)	
≤6 mo	0 (0)	1 (11.1)	
Subsequent aseptic revision, n (%)[d]	2 (3.2)	2 (14.3)	.152
Subsequent PJI, n (%)	3 (4.8%)	0 (0)	1.000
Subsequent PJI microorganism, n (%)			Not applicable
Same as UPC microorganism	0 (0)	Not applicable	
Mixed	1 (33.3)	Not applicable	
Different than UPC microorganism	2 (66.7)	Not applicable	

UPC, unexpected positive intraoperative culture; F, female; M, male; BMI, body mass index; ASA, American society of anesthesiologists; TKA, total knee arthroplasty; PJI, periprosthetic joint infection; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; *C. acnes*, *Cutibacterium acnes*; CNS, coagulase-negative *Staphylococcus* species; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; sp, species; IV, intravenous.

[a] Values are mean (standard deviation).

[b] Values are median (interquartile ranges).

[c] Reported as microorganism(s) grown from each intraoperative specimen that was positive (UPC).

[d] Subsequent aseptic revision after the study revision, censored out of survival analysis once occurs as subsequent PJI could be caused by subsequent aseptic revision.

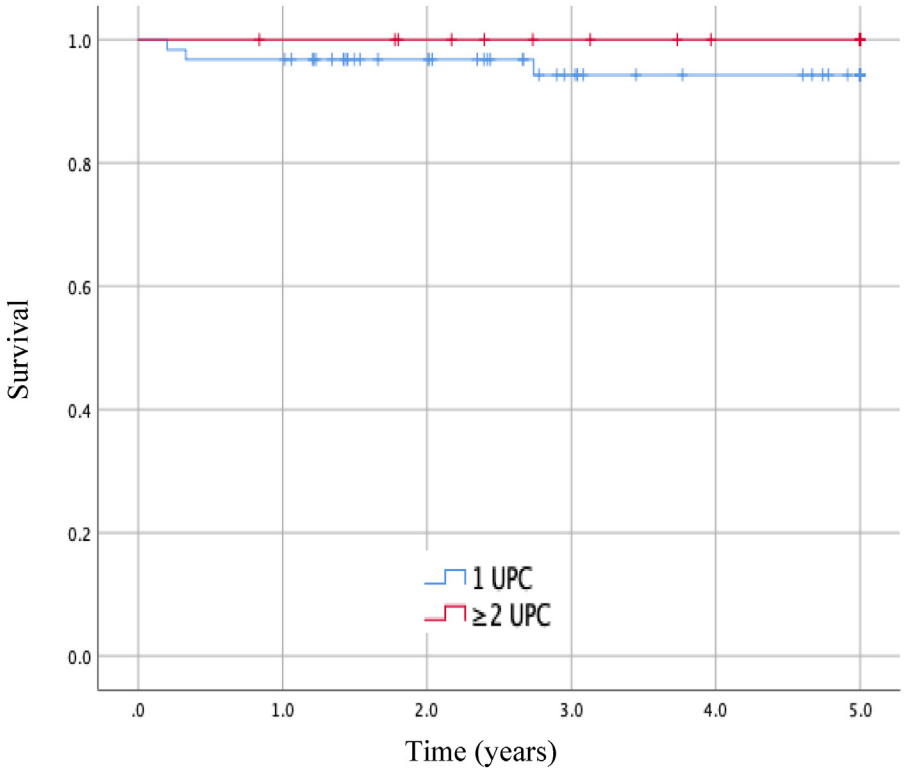

Fig. 4. Kaplan-Meier 5-year infection-free survival for the 1 versus ≥2 unexpected positive intraoperative culture (UPC) cohorts. Vertical spikes are censored data.

The vast majority of variables showed no statistical difference between the 1 UPC versus ≥2 UPC cohorts, however there was variability (Table 4). *C. acnes* was the most common microorganism in the single UPC cohort whereas methicillin-sensitive *Staphylococcus epidermidis* was in the ≥2 UPC cohort, and the proportions of microorganisms differed ($P = .029$). The ≥2 UPC cohort was more likely to receive antibiotic treatment (64.3% versus 29.0%, $P = .027$). The differences in route ($P = .123$) and duration ($P = .103$) of antibiotic treatment between cohorts were not statistically significant. All 3 of the subsequent PJIs were in the single UPC cohort ($P = 1.000$). However, the 5-year infection-free survival was similar for the 1 UPC versus ≥2 UPC cohorts, at 94.3% (95% CI 91.0% to 97.6%) and 100%, respectively ($P = .416$) (Fig. 4).

The majority of variables were statistically similar for the UPC cohorts that did versus did not receive antibiotic treatment, however important differences were noted (Table 5). The antibiotic treatment cohort had a higher proportion of ≥2 UPCs (33.3% versus 10.2%, $P = .027$). Differences in American Society of Anesthesiologists classification ($P = .078$), UPCs from swab samples ($P = .064$), UPCs from tissue samples ($P = .094$), UPC microorganisms ($P = .100$), and antibiotic resistant microorganisms ($P = .125$) between cohorts were not statistically significant. All 3 subsequent PJIs were in the antibiotic treatment cohort ($P = .042$) and the 5-year infection-free survival was worse for the antibiotic treatment cohort compared to the no antibiotic treatment cohort, at 87.4% (95% CI 80.5% to 94.3%) and 100%, respectively ($P = .021$) (Fig. 5). However, no patient with a single UPC without antibiotic treatment had a subsequent PJI-related implant failure. Of note, there were no recurrent infections in patients with ≥2 UPCs, but the majority received antibiotic treatment and numbers were low.

Discussion

Literature on the prevalence, clinical significance, and outcomes of UPC in presumed aseptic revision TKA is limited, with no clear consensus. By examining a large cohort from our institution, we sought to determine the prevalence of UPC and infection-free implant survival in this patient population.

The prevalence of 9.8% in our study is consistent with the mean prevalence of 10.5% (379/3,605) for revision total hip (THA) and TKA reported in a review of the literature (19). However, the reported prevalence varied substantially (4%-38%), only 111 TKA with UPC were included, and UPC in THA was twice more common than TKA [19]. This variability is due to significant heterogeneity between studies [19]. We included broth only UPCs because the specificity of these cultures has been shown to be high [21], and other studies have as well [15–17]. Studies that include a single UPC tend to report a higher incidence [17,22–24], however, this is not universal [15], and those reporting on ≥2 UPC vary as well [19]. Barrack et al [15] reported a prevalence of UPC in presumed aseptic revision TKA of 5.9% with 29/41 single UPCs, Saleh et al [17] reported 10% combined for TKA and THA including single UPCs, and Jacobs et al [16] reported 7.9% in TKA patients when only considering ≥2 UPC as significant. In our institution the prevalence of ≥2 UPC was only 1.8%. Our results support the indolent nature of microorganisms in UPC [15–17], however virulent and antibiotic resistant microorganisms did occur but were rare [17,19].

The 2- and 5-year infection-free survival for the entire UPC cohort was excellent at 97.4% and 95.3%, respectively. The causative microorganism in 2/3 of the subsequent PJIs was different than the UPC and the 5-year infection-free survival was outstanding (98.7%) when considering only infection-related failure caused by UPC

Table 5
Baseline, Demographic, Operative, Microbiological, Treatment, and Outcome Data for UPC Revisions Treated With Antibiotics Versus Those Not Treated With Antibiotics.

Variable	Antibiotic Treatment (n = 27)	No Antibiotic Treatment (n = 49)	*P* Value
Age (y)[a]	69.6 (9.9)	69.1 (8.5)	.808
Sex, F/M, n (%)	19/8 (70.4/29.6)	28/21 (57.1/42.9)	.256
BMI (kg/m^2)[b]	34.2 (29.3 to 39.5)	32.8 (27.9 to 37.7)	.259
ASA classification, n (%)			.078
1	0 (0)	0 (0)	
2	4 (14.8)	14 (28.6)	
3	21 (77.8)	35 (71.4)	
4	2 (7.4)	0 (0)	
Diabetes, n (%)	6 (22.2)	12 (24.5)	.824
Inflammatory condition, n (%)	4 (14.8)	6 (12.2)	.737
Etiology for primary TKA, n (%)			.737
Osteoarthritis	23 (85.2)	43 (87.8)	
Other	4 (14.8)	6 (11.2)	
Reasons for revision, n (%)			.684
Aseptic loosening	14 (51.9)	20 (40.8)	
Instability	7 (25.9)	15 (30.6)	
Arthrofibrosis	1 (3.7)	5 (10.2)	
Polyethylene wear ± osteolysis	3 (11.1)	1 (2.0)	
Patellar problem	1 (3.7)	3 (6.1)	
Pain no known source	1 (3.7)	3 (6.1)	
Periprosthetic fracture	0	1 (2.0)	
Pain component malposition	0	1 (2.0)	
History of prior TKA revision in study joint n (%)	3 (11.1)	8 (16.3)	.737
Age of prosthesis (y)[b]	10.9 (4.0 to 17.0)	8.6 (2.9 to 13.4)	.373
History of PJI in study joint, n (%)	1 (3.7)	1 (2.0)	1.000
Pre-operative serum CRP >10mg/L, n (%)	4 (14.8)	5 (10.2)	.714
Pre-operative serum ESR >30mm/h, n (%)	2 (7.4)	5 (10.2)	1.000
Preoperative joint aspirate, n (%)	8 (29.6)	16 (32.7)	.786
Type of revision, n (%)			.690
Patella	2 (7.4)	2 (4.1)	
Modular exchange	2 (7.4)	6 (12.2)	
1-component	4 (14.8)	4 (8.2)	
2-component	19 (70.4)	37 (75.5)	
Number of samples taken in study revision[b]	4 (3.0 to 5.0)	4 (3.0 to 5.0)	.485
1 UPC versus ≥ 2 UPC, n (%)			.027
1 UPC	18 (66.7)	44 (89.8)	
≥2 UPC	9 (33.3)	5 (10.2)	
UPC from swab sample, n (%)	22 (56.4)	20 (37.0)	.064
UPC from fluid sample, n (%)	0 (0)	1 (1.9)	1.000
UPC from tissue sample, n (%)	17 (43.6)	33 (61.1)	.094
UPC broth or solid, n (%)			.371
Broth	18 (46.2)	30 (55.6)	
Solid	21 (53.8)	24 (44.4)	
Microorganisms, n (%)[c]			.100
C. acnes	11 (24.4)	22 (38.6)	
Other CNS	11 (24.4)	12 (21.1)	
MSSE	14 (31.1)	8 (14.0)	
MRSE	1 (2.2)	0 (0)	
Streptococcus sp	2 (4.4)	6 (10.5)	
Enterococcus sp	3 (6.7)	1 (1.8)	
Others	3 (6.7)	8 (14.0)	
Number of revisions resistant UPC, n (%)	3 (11.0)	1 (2.0)	.125
Subsequent aseptic revision, n (%)	2 (7.4)	2 (4.1)	.612
Subsequent PJI, n (%)	3 (11.1)	0 (0)	.042
Subsequent PJI microorganism, n (%)[d]			Not applicable
Same as UPC microorganism	0 (0)	Not applicable	
Mixed	1 (33.3)	Not applicable	
Different than UPC microorganism	2 (66.7)	Not applicable	

UPC, unexpected positive intraoperative culture; F, female; M, male; BMI, body mass index; ASA, American society of anesthesiologists; TKA, total knee arthroplasty; PJI, periprosthetic joint infection; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; *C. acnes*, *Cutibacterium acnes*; CNS, coagulase-negative *Staphylococcus* species; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; sp, species.

[a] Values are mean (standard deviation).

[b] Values are median (interquartile ranges).

[c] Reported as microorganism(s) grown from each intraoperative specimen that was positive (UPC).

[d] Subsequent aseptic revision after the study revision, censored out of survival analysis once occurs as subsequent PJI could be caused by subsequent aseptic revision.

microorganism. Although subsequent PJIs caused by different microorganisms than the UPC likely represent a new infection, it is plausible that these microorganisms were present during the study revision but missed due to the limited sensitivity of cultures in PJI [25]. A high proportion of subsequent PJI caused by a different microorganism than the UPC is common, however factors associated with re-infection by the same microorganism have been identified [12,16,17,19]. Our results were consistent with the

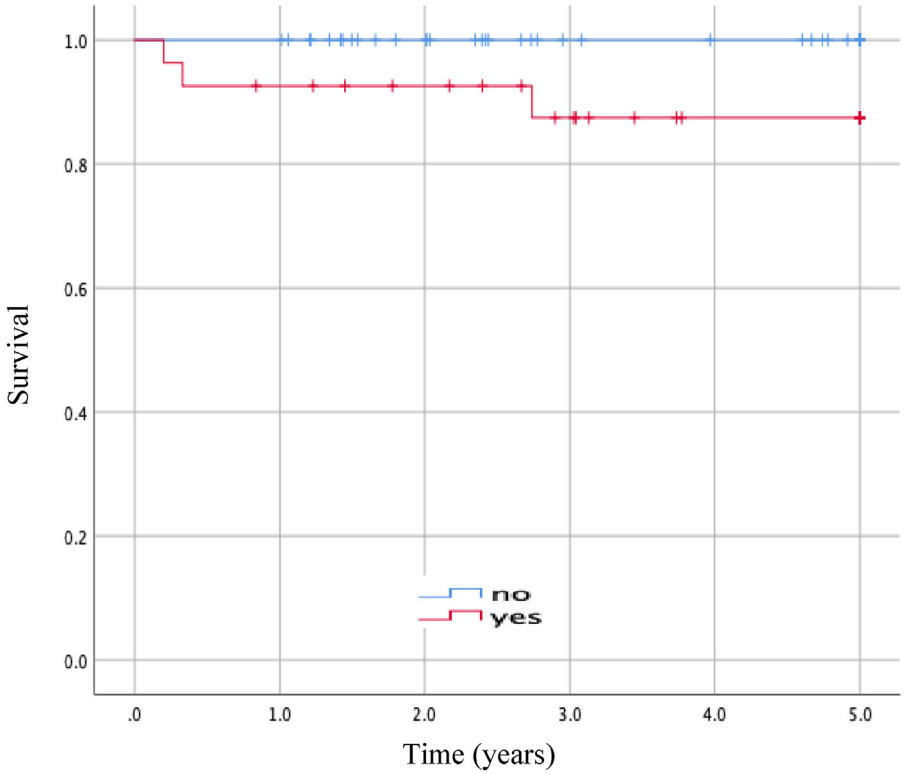

Fig. 5. Kaplan-Meier 5-year infection-free survival for the unexpected positive intraoperative culture cohort treated with antibiotics (yes) versus not treated with antibiotics (no). Vertical spikes are censored data.

majority of literature [16,17,19,23,24,26], however, only 2 studies report the survival of TKA separate from THA [15,16], and most studies reporting similar survival were limited by short term follow-up or used advanced molecular or sonification techniques [12,24,27,28]. Barrack et al [15] reported that only 2/41 of presumed aseptic TKA revisions with UPC went onto subsequent PJI. However, Jacobs et al [16] showed a 2-year survival of 88% in 17 TKA with ≥2 UPC, lower than that of the true aseptic TKA cohort.

Our infection-free survival was similar for the 1 UPC versus ≥2 UPC cohorts. This must be interpreted with caution due to differences between cohorts (microorganisms, antibiotic treatment). In addition, all of the subsequent infections were in the 1 UPC cohort, which is contrary to most literature [15,19,29], but not all [17]. Possible explanations for this in our study include differences in the proportion treated with antibiotics and causative microorganisms, the high proportion of 2-component revisions, the low sample size of the ≥2 UPC cohort, or other differences between cohorts not accounted for due to the retrospective nature of the study. In addition, the higher proportion of antibiotic treatment in the ≥2 UPC cohort may have significantly improved the infection-free survival.

Treatment protocols vary considerably in the literature [15,19,26]. In our study only 35.5% (27) of patients received antibiotic treatment for their UPC(s), and of these, 92.6% (25) were treated for ≤6 weeks. Surprisingly, the infection-free survival was worse for the antibiotic treatment cohort. Similar results have been reported [12,26], however, one can't conclude that antibiotic treatment is associated with a higher risk of subsequent PJI based on our data. Differences between cohorts, lack of a standardized UPC treatment protocol, and the retrospective nature of our study introduced a selection bias for those treated with antibiotics. Patients treated with antibiotics likely shared a higher degree of clinical suspicion for PJI or other factors that influenced clinicians to treat medically. The worse survival of the antibiotic treatment cohort may reflect that those treated with antibiotics were more likely to be true PJI as compared to noninfected cases.

Several studies excluded revisions with only a single UPC [16,19,26], while others have questioned their clinical significance [15,19,23]. No patient in our study with a single UPC deemed not to require antibiotic treatment had a subsequent PJI-related implant failure. These results suggest that a single UPC without signs of infection is likely a contaminant and does not require antibiotic treatment, and support the conclusions of Barrack et al [15]. We are unable to draw any meaningful conclusions on antibiotic treatment and the significance of all ≥2 UPC in presumed aseptic revisions, however it has been shown that even a single UPC with a high virulence microorganism in a patient not meeting Musculoskeletal Infection Society criteria may represent an infection and require antibiotic treatment [17].

Our study has several limitations. Lack of a standardized UPC treatment protocol, preoperative PJI screening protocol, and the retrospective design of this study is subject to associated biases, most of which are discussed above. Frozen sections are not routinely sent during aseptic revisions at our institution. It is possible that utilization of intraoperative frozen sections may have impacted UPC number. Common to most of the UPC literature, the type and number of intraoperative samples taken for culture was not standardized and both are important in detecting microorganisms and PJI [22,30,31]. This in an important confounding factor to consider when interpreting our results as allocation of cases into study cohorts may have been affected. However, the majority of our cohort had an extended anerobic incubation time of 10 days [32]. Our study had no exclusions for death or inadequate/loss to follow-up, but not all patients were at the survival analysis time endpoints from the study revision surgery. Patients can be to be lost to follow-up at tertiary care centers, however when revisions we perform have complications, they are sent back to us for management or at

minimum we are notified. Lastly, our study was underpowered to detect differences between cohorts for secondary outcomes of interest. Although encouraging, our low event rate ($n = 3$) prohibited use of regression analysis to identify factors associated with subsequent infection-related failure. Nevertheless, this study is the largest series of UPC in TKA in the literature, does not confound TKA results with those of THA [16], and inclusion of a single UPC provides data on a common and clinically relevant challenge for clinicians.

In conclusion, the prevalence of UPC in presumed aseptic revision TKA is 9.8% and the 2- and 5-year infection-free survival is excellent. Infection-free survival when only considering subsequent PJI caused by the same UPC microorganism is outstanding. The majority of subsequent PJI-related failures were caused by a different microorganism than the UPC. Infection-related survival was similar between the 1 and $\geq$2 UPC cohorts and the cohort treated with antibiotics had an inferior survival compared to those not treated with antibiotics. However, these findings must be interpreted with caution due to selection biases and study limitations. Patients with a single UPC deemed not to require antibiotic treatment had no subsequent PJI-related implant failures, strongly suggesting that a single UPC without signs of infection is likely a contaminant and does not require antibiotic treatment.

References

[1] Singh JA, Yu S, Chen L, Cleveland JD. Rates of total joint replacement in the United States: future projections to 2020-2040 using the national inpatient sample. J Rheumatol 2019;46:1134–40. https://doi.org/10.3899/jrheum.170990.

[2] Canadian Institute for Health Information. Hip and Knee Replacements in Canada, 2017-2018. Canadian Joint Replacement Registry Annual Report; 2019. https://secure.cihi.ca/free_products/cjrr-annual-report-2019-en-web.pdf [accessed 14.01.21].

[3] Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007;89:780–5. https://doi.org/10.2106/jbjs.F.00222.

[4] Labek G, Thaler M, Janda W, Agreiter M, Stockl B. Revision rates after total joint replacement: cumulative results from worldwide joint register datasets. J Bone Joint Surg Br 2011;93:293–7. https://doi.org/10.1302/0301-620x.93b3.25467.

[5] Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. Lancet 2016;387:386–94. https://doi.org/10.1016/S0140-6736(14)61798-0.

[6] Kapadia BH, McElroy MJ, Issa K, Johnson AJ, Bozic KJ, Mont MA. The economic impact of periprosthetic infections following total knee arthroplasty at a specialized tertiary-care center. J Arthroplasty 2014;29:929–32. https://doi.org/10.1016/j.arth.2013.09.017.

[7] Kurtz SM, Lau E, Watson H, Schmier JK, Parvizi J. Economic burden of periprosthetic joint infection in the United States. J Arthroplasty 2012;27:61–65.e1. https://doi.org/10.1016/j.arth.2012.02.022.

[8] Kurtz SM, Lau EC, Son MS, Chang ET, Zimmerli W, Parvizi J. Are we winning or losing the battle with periprosthetic joint infection: trends in periprosthetic joint infection and mortality risk for the medicare population. J Arthroplasty 2018;33:3238–45. https://doi.org/10.1016/j.arth.2018.05.042.

[9] Parvizi J, Zmistowski B, Berbari EF, Bauer TW, Springer BD, Della Valle CJ, et al. New definition for periprosthetic joint infection: from the workgroup of the musculoskeletal infection society. Clin Orthop Relat Res 2011;469:2992–4. https://doi.org/10.1007/s11999-011-2102-9.

[10] Parvizi J, Gehrke T. Definition of periprosthetic joint infection. J Arthroplasty 2014;29:1331. https://doi.org/10.1016/j.arth.2014.03.009.

[11] 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.

[12] Fernandez-Sampedro M, Salas-Venero C, Farinas-Alvarez C, Sumillera M, Perez-Carro L, Fakkas-Fernandez M, et al. Postoperative diagnosis and outcome in patients with revision arthroplasty for aseptic loosening. BMC Infect Dis 2015;15:232. https://doi.org/10.1186/s12879-015-0976-y.

[13] Parvizi J, Suh DH, Jafari SM, Mullan A, Purtill JJ. Aseptic loosening of total hip arthroplasty: infection always should be ruled out. Clin Orthop Relat Res 2011;469:1401–5. https://doi.org/10.1007/s11999-011-1822-1.

[14] Wasko MK, Goodman SB. Emperor's new clothes: is particle disease really infected particle disease? J Orthop Res 2016;34:1497–504. https://doi.org/10.1002/jor.23292.

[15] Barrack RL, Aggarwal A, Burnett RS, 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.

[16] Jacobs AME, Benard M, Meis JF, van Hellemondt G, Goosen JHM. The unsuspected prosthetic joint infection : incidence and consequences of positive intra-operative cultures in presumed aseptic knee and hip revisions. Bone Joint J 2017;99-B:1482–9. https://doi.org/10.1302/0301-620x.99b11.Bjj-2016-0655.R2.

[17] 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.

[18] Segawa H, Tsukayama DT, Kyle RF, Becker DA, Gustilo RB. Infection after total knee arthroplasty. A retrospective study of the treatment of eighty-one infections. J Bone Joint Surg Am 1999;81:1434–45.

[19] 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 2019;17:1–6. https://doi.org/10.1016/j.jor.2019.06.028.

[20] 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.

[21] Smith EB, Cai J, Wynne R, Maltenfort M, Good RP. Performance characteristics of broth-only cultures after revision total joint arthroplasty. Clin Orthop Relat Res 2014;472:3285–90. https://doi.org/10.1007/s11999-014-3507-z.

[22] Atkins BL, Athanasou N, Deeks JJ, Crook DW, Simpson H, Peto TE, et al. Prospective evaluation of criteria for microbiological diagnosis of prosthetic-joint infection at revision arthroplasty. The OSIRIS Collaborative Study Group. J Clin Microbiol 1998;36:2932–9.

[23] Dramis A, Aldlyami E, Grimer RJ, Dunlop DJ, O'Connell N, Elliott T. What is the significance of a positive propionibacterium acnes culture around a joint replacement? Int Orthop 2009;33:829–33. https://doi.org/10.1007/s00264-008-0534-y.

[24] Kempthorne JT, Ailabouni R, Raniga S, Hammer D, Hooper G. Occult infection in aseptic joint loosening and the diagnostic role of implant sonication. Biomed Res Int 2015;2015:946215. https://doi.org/10.1155/2015/946215.

[25] Yoon H-K, Cho S-H, Lee D-Y, Kang B-H, Lee S-H, Moon D-G, et al. A review of the literature on culture-negative periprosthetic joint infection: epidemiology, diagnosis and treatment. Knee Surg Relat Res 2017;29:155–67. https://doi.org/10.5792/ksrr.16.034.

[26] Marculescu CE, Berbari EF, Hanssen AD, Steckelberg JM, Osmon DR. Prosthetic joint infection diagnosed postoperatively by intraoperative culture. Clin Orthop Relat Res 2005;439:38–42.

[27] Ince A, Rupp J, Frommelt L, Katzer A, Gille J, Lohr JF. Is "aseptic" loosening of the prosthetic cup after total hip replacement due to nonculturable bacterial pathogens in patients with low-grade infection? Clin Infect Dis 2004;39:1599–603. https://doi.org/10.1086/425303.

[28] Moojen DJF, Van Hellemondt G, Vogely HC, Burger BJ, Walenkamp GHIM, Tulp NJA, et al. Incidence of low-grade infection in aseptic loosening of total hip arthroplasty: a prospective multicenter study using extensive routine and broad-range 16S PCR with reverse line blot diagnostics. Acta Orthop 2010;81:667–73. https://doi.org/10.3109/17453674.2010.525201.

[29] 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.

[30] Aggarwal VK, Higuera C, Deirmengian G, Parvizi J, Austin MS. Swab cultures are not as effective as tissue cultures for diagnosis of periprosthetic joint infection. Clin Orthop Relat Res 2013;471:3196–203. https://doi.org/10.1007/s11999-013-2974-y.

[31] Bémer P, Léger J, Tandé D, Plouzeau C, Valentin AS, Jolivet-Gougeon A, et al. How many samples and how many culture media to diagnose a prosthetic joint infection: a clinical and microbiological prospective multicenter study. J Clin Microbiol 2016;54:385–91. https://doi.org/10.1128/JCM.02497-15.

[32] Butler-Wu SM, Burns EM, Pottinger PS, Magaret AS, Rakeman JL, Matsen FA, et al. Optimization of periprosthetic culture for diagnosis of propionibacterium acnes prosthetic joint infection. J Clin Microbiol 2011;49:2490–5. https://doi.org/10.1128/JCM.00450-11.