Unexpected positive cultures in aseptic revision hip and knee arthroplasty

prevalence and outcomes at mid-term follow-up

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Aims

The outcomes of patients with unexpected positive cultures (UPCs) during revision total hip arthroplasty (THA) and total knee arthroplasty (TKA) remain unknown. The objectives of this study were to establish the prevalence and infection-free implant survival in UPCs during presumed aseptic single-stage revision THA and TKA at mid-term follow-up.

Methods

This study included 297 patients undergoing presumed aseptic single-stage revision THA or TKA at a single treatment centre. All patients with at least three UPCs obtained during revision surgery were treated with minimum three months of oral antibiotics following revision surgery. The prevalence of UPCs and causative microorganisms, the recurrence of periprosthetic joint infections (PJIs), and the infection-free implant survival were established at minimum five years' follow-up (5.1 to 12.3).

Results

Of the 297 patients undergoing aseptic revisions, 37 (12.5%) had at least three UPCs obtained during surgery. The UPC cohort included 23 males (62.2%) and 14 females (37.8%), with a mean age of 71.2 years (47 to 82). Comorbidities included smoking (56.8%), hypertension (48.6%), diabetes mellitus (27.0%), and chronic renal impairment (13.5%). The causative microorganisms included *Staphylococcus epidermidis* (49.6%), *Bacillus* species (18.9%), *Micrococcus* species (16.2%), and *Cutibacterium acnes* (16.2%). None of the study patients with UPCs developed further PJIs or required further surgical intervention during follow-up.

Conclusion

The prevalence of UPCs during presumed aseptic revision THA and TKA was 12.5%. The most common causative microorganisms were of low virulence, and included *S. epidermidis*, *Bacillus* species, *Micrococcus* species, and *C. acnes*. Microorganism-specific antibiotic treatment for minimum three months' duration of UPCs in presumed aseptic revision arthroplasty was associated with excellent infection-free implant survival at mid-term follow-up.

Take home message

- The prevalence of unexpected positive cultures (UPCs) during presumed aseptic revision total hip arthroplasty and total knee arthroplasty was 12.5%.
- Microorganism-specific antibiotic treatment for minimum three months' duration following presumed aseptic revision arthroplasty with UPCs was associated with excellent infection-free implant survival at mid-term follow-up.

Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) have developed into highly successful surgical procedures

for the treatment of symptomatic hip and knee arthritis respectively.[1,2] However, periprosthetic joint infection (PJI) following arthroplasty is a devastating complication, with an incidence of 1% to 2% following primary THA and TKA, and 3% to 10% following revision THA and TKA.[3-6] The overall incidence of PJIs continues to increase owing to more arthroplasty procedures being undertaken annually, and the rising prevalence of comorbidities such as obesity, diabetes, chronic renal disease, and immunosuppression within the population.[4,7] PJIs have a major impact on the patient's physical and mental health, with five-year mortality rates now similar to oncology patients.[4] Furthermore, PJIs place a significant economic burden on the healthcare system, and as the demands for primary and revision arthroplasty are expected to increase in the next two decades, this financial burden will likely increase further.[4] Early identification and timely treatment of PJI are crucial for eliminating the infection and optimizing long-term component survival.[8,9]

Accurate preoperative diagnosis of PJI is essential, as the presence of an active infection leads to significant changes in the subsequent therapeutic procedures.[2,10] However, there remains no uniform consensus on the optimal management of presumed PJI, with various guidelines on the ideal investigative algorithms, imaging methods, serum tests, and synovial markers to diagnose PJIs.[11-14] It has been suggested that some presumed aseptic failures following revision arthroplasty may be attributable to undiagnosed PJI.[15-17] Additionally, some patients with negative preoperative investigations for PJI may sometimes have unexpected positive cultures (UPCs) obtained during presumed aseptic revision arthroplasty. This situation is also known as a 'positive intraoperative culture' or 'type 1 infection', and poses a significant challenge as the treatments for infection and aseptic loosening differ from one another.[11,18] The true prevalence and outcomes of UPCs in presumed aseptic revision arthroplasty remain undetermined due to heterogeneity among existing studies in relation to the diagnostic criteria for PJI, the number of intraoperative tissue samples obtained, and duration of postoperative antibiotics.[11,19-23]

The objectives of this study were to establish the prevalence and infection-free implant survival in UPCs during presumed aseptic single-stage revision THA and TKA at mid-term follow-up.

Methods

This study included all patients undergoing presumed aseptic revision THA or TKA at a single tertiary referral centre between July 2011 and February 2018.

The inclusion criteria were as follows: patient was aged 18 to 80 years; single-stage revision THA or TKA was performed for aseptic loosening; intraoperative culture samples were obtained during revision surgery; and minimum follow-up period was five years after revision arthroplasty.

The exclusion criteria were as follows: PJI was confirmed or suspected before revision surgery; previous revision surgery for any reason (including the first of a two-stage revision arthroplasty for PJI); intraoperative findings were consistent with PJI; and/or intraoperative cultures were not obtained or available for analysis. In total, 297 patients matched the inclusion and exclusion criteria, and the results of this cohort formed the base cohort for the study population. Minimum follow-up time following revision surgery was five years (5.1 to 12.3).

The study was reviewed by the hospital review board (University College London Hospital NHS Trust, London, UK), who advised that further research ethics committee approval was not required.

Preoperative evaluation in all patients included clinical examination for PJI and measurement of serum white cell count, CRP, and ESR. If there were any clinical or biochemical concerns for PJI, the operating surgeon performed a joint aspiration under sterile conditions. All revision TKAs were performed using the medial parapatellar approach. The existing components and cement were removed in a bone-conserving manner using thin osteotomes, an oscillating saw, a Gigli saw, and a high-speed burr. Both the proximal tibial and distal femoral resections were refashioned using intramedullary referencing. The femoral rotation was confirmed using the transepicondylar axis and the anteroposterior, chamfer, and notch cuts were performed. The tibial rotation was established with the trial components in place. The tibial and patellar components were prepared and the final components were implanted. In all 147 patients undergoing revision TKA, the femoral and tibial components were revised using antibiotic-impregnated bone cement. Up until December 2016, powdered gentamycin was used with 1 gm to 2 gm of vancomycin added per 40 gm of cement. After 2016, Palacos with gentamycin already inside was used with 1 to 2 gm of vancomycin added per 40 gm of cement.

All revision THAs were performed using the posterior approach. The acetabular component was removed using curved osteotomes and the Explant acetabular component removal system (Zimmer Bi0met, USA). The femoral component was removed using a pencil-tip burr, chisels, thin osteotomes, and a universal femoral stem extraction system. Residual cement in the canal was removed using chisels and curettes. If required, the distal cement plug was removed using a drill bit to perforate the plug, a guide wire with sequentially larger reamers, and a reverse hook. Of the 150 patients undergoing revision THA, 101 had revision of both the acetabular and femoral components, 22 had revision of the acetabular component only, and 27 had revision of the femoral stem only. All revision THAs were performed with cementless implants.

During revision surgery, a minimum of five (range 5 to 8) intraoperative tissue samples were taken using separate sterile forceps and scalpels for each sample. In the study centre, a minimum of five intraoperative soft-tissue samples were the standard practice, with further specimens recommended from any tissues that appeared clinically suspicious for PJI. All soft-tissue samples were plated and incubated at 35°C aerobically on 5% sheep blood and chocolate agar plates and anaerobically on 5% sheep blood and fastidious anaerobic agar plates. Cultures were continued for 14 days or until flagged as positive. All patients received one prophylactic dose of intravenous cefuroxime and gentamycin after the soft-tissue specimens had been retrieved, and two further doses of intravenous cefuroxime at eight hours and 16 hours after revision surgery.

The definition of UPC was the presence of three or more intraoperative soft-tissue samples positive for the growth of at least one microorganism on either solid or

broth medium. Patients with UPCs received microorganism-specific intravenous antibiotics initially for three to five days and oral antibiotics for a minimum period of three months following revision surgery. Antibiotics were selected on the sensitivities of the microorganism grown, each patient's medical profile including comorbidities and allergies, and Trust guidelines using data on local microorganism resistance. After this period, all patients were reviewed by the operating surgeon (FSH) to ensure there were no clinical signs of PJI and normalization of serum white cell count, CRP, and ESR. Recurrence of PJI was defined as the presence of infection requiring antibiotics or any surgical intervention (including wound washout; debridement, antibiotics, and implant retention; and revision arthroplasty or amputation) around the revised arthroplasty following the index revision procedure. All patients with UPCs were managed as part of the infection arthroplasty multidisciplinary team. This included an infectious disease consultant with a specialist interest in orthopaedics. The infectious disease team reviewed all patients with UPCs in the outpatient department for 12 months after surgery.

Study data are presented with absolute numbers and percentages where appropriate. Due to the limited number of patients with UPCs, it was not suitable to undertake more advanced statistical analyses with computer algorithms to model the probability of obtaining UPCs or establish independent risk factors for UPCs during revision THA and TKA.

Results

Of the 297 patients who underwent aseptic single-stage revisions, 37 (12.5%) had UPCs. This group consisted of 23 males (62.2%) and 14 females (37.8%), with a mean age of 71.2 years (47 to 82) and a mean BMI of 31.1 kg/m^2 (24 to 37) at time of revision surgery. The mean time interval between the index arthroplasty and revision arthroplasty was 8.1 years (0.6 to 15.1).

The index arthroplasty was performed for osteoarthritis in 30 patients (81.1%), trauma in three patients (8.1%), avascular necrosis in two patients (5.4%), and inflammatory arthropathy in two patients (5.4%) (Table I). Medical comorbidities included hypertension in 18 patients (48.6%), diabetes mellitus in ten patients (27.0%), and chronic renal impairment in five patients (13.5%). A total of 21 patients (56.8%) were current smokers or previous smokers.

Microbiological analysis of the UPCs revealed that the causative organism was *Staphylococcus epidermidis* in 18 patients (49.6%), *Bacillus* species in seven patients (18.9%), *Micrococcus* species in six patients (16.2%), and *Cutibacterium acnes* in six patients (16.2%). All patients with UPCs completed three months of oral antibiotics following revision surgery. Of note, two immunosuppressed patients received six months of postoperative intravenous antibiotic treatment due to their poor immune status and increased risk of PJI recurrence.

None of the study patients had recurrence of the PJI and none required further antibiotic treatment or any surgical intervention at minimum five years' (5.1 to 12.3) follow-up.

Table I. Demographics and baseline characteristics of patients with unexpected positive cultures from tissue specimens obtained during presumed aseptic revision total hip arthroplasty and total knee arthroplasty.

Demographic/baseline character	Outcomes
Mean age at time of surgery, yrs (range)	71.2 (47 to 82)
Sex F:M, n (%)	14 (37.8):23 (62.2)
Mean time from index arthroplasty, yrs (range)	8.1 (0.6 to 15.1)
Index diagnosis, n (%)	
Osteoarthritis	30 (81.1)
Trauma	3 (8.1)
Avascular necrosis	2 (5.4)
Inflammatory arthropathy	2 (5.4)
Mean BMI, kg/m^2 (range)	31.1 (24 to 37)
ASA grade,[24] n (%)	
I	2 (5.5)
II	20 (54.1)
III	15 (40.5)
IV	0 (0.0)
Comorbidities, n (%)	
Smoking	21 (56.8)
Hypertension	18 (48.6)
Diabetes	10 (27.0)
Renal failure	5 (13.5)

ASA, American Society of Anesthesiologists; UPC, unexpected positive cultures.

Discussion

This study found that the prevalence of UPCs during presumed aseptic revision THA and TKA was 12.5%. The most common causative microorganisms were of low virulence, and included *S. epidermidis, Bacillus* species, *Micrococcus* species, and *C. acnes*. Microorganism-specific antibiotic treatment for minimum three months' duration following presumed aseptic revision arthroplasty with UPCs was associated with excellent infection-free implant survival at mid-term follow-up.

The prevalence of UPCs during presumed aseptic revision of THAs and TKAs in this study was comparable to the reported values from previous studies.[11,15,19–21,23,25–28] Purudappa et al[29] conducted a systematic review using data from ten studies and reported that UPCs were present in 379 patients (10.5%) from 3,605 patients undergoing revision for presumed aseptic THA and TKA. The authors noted that the prevalence of UPCs during presumed aseptic revision arthroplasty ranged from 4% to 38%, which reflected interstudy heterogeneity in relation to the following: 1) diagnostic criteria for PJI; 2) choice and duration of prophylactic antibiotics; 3) microbiological sample culture techniques; and 4) duration of postoperative antibiotic treatment. In the current study, preoperative diagnostic investigations included clinical examination and blood tests, with a low threshold for joint aspiration if there was any suspicion of PJI. This may have helped to improve preoperative PJI diagnostic accuracy and obtain UPC prevalence towards the more favourable range reported within the existing literature.

An important area of controversy is the number of UPCs required during presumed aseptic revision arthroplasty required to diagnose PJI. Berend et al[19] and Neufeld et al[28] diagnosed PJI with a single positive UPC, Segawa et al[30] diagnosed PJI using two positive UPCs, and Saleh et al[20] stratified the risk of PJI based on the number of UPCs using the Musculoskeletal Infection Society (MSIS) criteria.[12,13] Recently, Neufeld et al[28] reviewed outcomes in 110 UPCs from 1,196 aseptic revision THAs and found that no patient with a single UPC that was not treated with antibiotics developed PJI caused by the UPC-identified organism. The authors suggested that in the absence of other signs of PJI, a single UPC did not require antibiotic treatment. The current study used at least three UPCs to diagnose PJI instead of at least two positive samples as suggested by the 2012 MSIS criteria and 2021 European Bone and Joint Infection Society (EBJIS) guidelines as the use of at least three UPCs has been shown to minimize the inclusion of false positive cultures in diagnosing PJIs.[12,13,31,32]

The findings of this study are consistent with previous trials showing that UPCs are commonly caused by low-virulent microorganisms.[11,18,19,30] Tsukayama et al[18] reviewed outcomes in 97 patients with UPCs obtained during revision THA for aseptic loosening and reported that gram-positive cocci accounted for 74% of the isolates, gram-negative bacilli for 14%, and anaerobes for 8%. Similarly, Saleh et al[20] reviewed outcomes in 155 UPCs from 1,540 revision THAs and TKAs for aseptic loosening and reported that 67% of infections were caused by coagulase-negative staphylococci and *C. acnes*. Marculescu et al[22] reviewed outcomes in 16 patients with UPCs obtained during presumed aseptic revision arthroplasty, and found that 50% of cases were attributed to coagulase-negative staphylococci and 25% of cases were attributed to *C. acnes*. These low-virulence microorganisms may evade detection on preoperative diagnostic testing for PJI as they remain clinically dormant and limit the associated systemic inflammatory response. Molecular testing with broad-range 16 S rRNA polymerase chain reaction with reverse line blot hybridization technique may help to improve diagnostic accuracy compared with pathological analysis and tissue cultures.[21]

There remains significant heterogeneity in the route and duration of antibiotic treatment for UPCs obtained during presumed aseptic revision arthroplasty.[11,22,23,26,27] Marculescu et al[22] followed 16 patients with UPCs obtained during aseptic revision arthroplasty and reported a five-year implant survival of 89%. However, 12 patients received intravenous antibiotics for a median duration of 28 days; eight of these patients received oral antibiotic suppression treatment for a median duration of 876 days, and three patients received no antibiotic treatment at all. The excellent survival in our study may be attributed to all patients receiving minimum three months of oral antibiotics, and six months of intravenous antibiotics for high-risk patients that were immunocompromised. Our findings are supported by Berend et al,[19] who treated all patients with UPCs with oral antibiotics for positive gram stains and intravenous antibiotics for positive cultures and reported 100% implant survival. Although our study shows excellent outcomes with minimum three months of antibiotics, we would advise caution in translating these findings to UPCs with high virulence or multidrug-resistant microorganisms, in which the risk of PJI may be increased.

There are several important limitations of this study that need to be acknowledged when interpreting the findings. This was a retrospective study, with the inherent biases and limitations of this study design. Due to the limited number of UPCs and the absence of PJIs following the index revision surgery, it was not possible to stratify outcomes based on the number of intraoperative UPCs or to identify individual risk factors associated with PJI recurrence. The study did not record any patient-reported outcome scores and none of the study patients had joint aspirations to help exclude subclinical PJI at final follow-up. However, the study provides an important evidence base for the management of UPCs, which represent a challenging issue that is commonly encountered during presumed aseptic revision arthroplasty.

In conclusion, the prevalence of UPCs during presumed aseptic revision THA and TKA was 12.5%. The most common causative microorganisms were of low virulence, and included *S. epidermidis, Bacillus* species, *Micrococcus* species, and *C. acnes*. Microorganism-specific antibiotic treatment for minimum three months' duration following presumed aseptic revision arthroplasty with UPCs was associated with excellent infection-free implant survival at mid-term follow-up.

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Data sharing

The data that support the findings for this study are available to other researchers from the corresponding author upon reasonable request.

Ethical review statement

The study was reviewed by the hospital review board, who advised that further research ethics committee approval was not required.

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