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Change in organism between first- and second-stage revision for periprosthetic joint infection of knee arthroplasty independently associated with increased risk of failure

A TWO-CENTRE STUDY

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Aims

Achievement of accurate microbiological diagnosis prior to revision is key to reducing the high rates of persistent infection after revision knee surgery. The effect of change in the microorganism between the first- and second-stage revision of total knee arthroplasty for periprosthetic joint infection (PJI) on the success of management is not clear.

Methods

A two-centre retrospective cohort study was conducted to review the outcome of patients who have undergone two-stage revision for treatment of knee arthroplasty PJI, focusing specifically on isolated micro-organisms at both the first- and second-stage procedure. Patient demographics, medical, and orthopaedic history data, including postoperative outcomes and subsequent treatment, were obtained from the electronic records and medical notes.

Results

The study cohort consisted of 84 patients, of whom 59.5% (n = 50) had successful eradication of their infection at a mean follow-up of 4.7 years. For the 34 patients who had recurrence of infection, 58.8% (n = 20) had a change in isolated organism, compared to 18% (n = 9) in the infection eradication group ($p < 0.001$). When adjusting for confound, there was no association when the growth on the second stage was the same as the first (odd ratio (OR) 2.50, 95% confidence interval (CI) 0.49 to 12.50; $p = 0.269$); however, when a different organism was identified at the second stage, this was independently associated with failure of treatment (OR 8.40, 95% CI 2.91 to 24.39; $p < 0.001$). There were no other significant differences between the two cohorts with regard to patient demographics or type of organisms isolated.

Conclusion

Change in the identified microorganism between first- and second-stage revision for PJI was associated with failure of management. Identification of this change in the microorganism prior to commencement of the second stage may help target antibiotic management and could improve the success of surgery in these patients.

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Introduction

The prevalence of persistent or recurrent infection following two-stage exchange arthroplasty following failure of a total knee arthroplasty (TKA) has been reported to be 10% to 25%.[1-5] As more knee arthroplasties are being performed in younger patients, and life expectancy is also increasing, it is anticipated that a greater number of infected joint arthroplasties will need to be managed.[6,7] Furthermore, improvements in implant machinery, polyethylene wear rates, and surgical technique will result in a decline in revision associated with aseptic loosening or wear, and may see periprosthetic joint infection (PJI) become the leading cause of revision procedures.[8]

Failure to control infection in these patients or recurrent infection can have morbid consequences, with prolonged hospital stay, multiple subsequent operations, and protracted courses of antibiotics, with no guarantee of a successful outcome.[9] Regardless of treatment approach, significant rates of mortality have been reported in these patients.[10] Patients in whom two-stage exchange arthroplasty has failed present as a heterogenous cohort with respect to patient and surgical demographics make comparison challenging.[11] Known risk factors for failure after two-stage exchange arthroplasty include polymicrobial infection, obesity, chronic lymphoedema, number of surgical procedures, size of bone defects, and drug-resistant organisms.[12-15] The available literature on repeat two-stage revisions for TKA infection is based on small cohorts or single centres reporting variable success rates and varying follow-up periods.[8,10,16–19]

Kim et al[20] have contended that culture outcome (positive vs negative) does not influence the outcome from two-stage revision, as measured by the likelihood of further surgical intervention. However, Yang et al[21] demonstrated that prolonged postoperative microorganism directed antibiotics following two stage revision TKAs is associated with a significantly reduced likelihood of further infection. This may therefore indicate that the presence and subsequent directed eradication of microorganisms at reimplantation may improve survivorship.

The aim of the current study was to assess the success of two-stage revision for treatment of knee arthroplasty for PJI of patients managed at two orthopaedic units (The Freeman Hospital and Royal Infirmary of Edinburgh, UK), and the effect of positive growth at the second stage.

Methods

A retrospective cohort study was undertaken to investigate the outcome of two-stage revision arthroplasty for treatment of TKA infection across two orthopaedic units focusing on the influence of a change in causative organism on postoperative successful infection eradication.

This study examined the outcome for a consecutive cohort of patients between 2008 and 2021 who had undergone knee revision surgery for infection by interrogation of the hospital surgical coding systems. This patient cohort was then cross-referenced with the microbiology laboratory reports to collate data on the intraoperative samples sent and the final culture result, for both at the first and second stages. The diagnosis of knee PJI was defined as documentation of the diagnosis in medical records by the treating surgical team, made using a combination of symptoms, examination findings, serological markers, and radiological appearances. Patient records were reviewed to collect demographic data, including age at first-stage procedure, sex, past medical history (specifically risk factors for infection), and orthopaedic history, including previous revision surgeries, then the outcome following the two-stage revision.

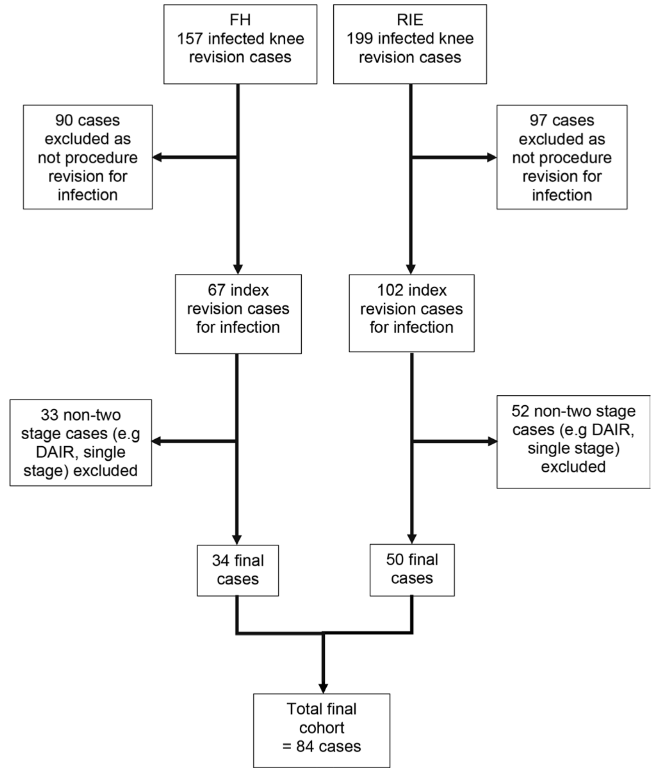

Fig. 1

Identification of the final patient cohort.

Figure 1 shows how the final cohort of 84 patients was identified. The patients were then subdivided as per their postoperative outcome into either successful eradication of the infection (i.e. required no further long-term medical or surgical management), or failure of treatment, including suppressive antibiotics or further surgical intervention (debridement, repeat two-stage revision, or salvage procedures (i.e. fusion or amputation)). A comparison was then made between the two outcome groups, specifically with regards to the consistency of reporting for culture results at each stage.

Statistical analysis. An independent *t*-test was used to compare linear variables between groups. Dichotomous variables were assessed using a chi-squared test. Logistic regression was used to adjust for confounding to identify factors associated with failure of treatment. A p-value < 0.05 was defined as statistically significant.

Ethical declaration. The authors conducted a retrospective service evaluation; as such, there was no additional patient contact and no requirement for formal ethical approval. The project was registered with the institutions audit department (NE registration number 7851. RIE Research Ethics Committee, South-East Scotland Research Ethics Service, Scotland 11/AL/0079, 16/SS/0026), and was conducted in accordance with the Declaration of Helsinki and the guidelines for good clinical practice.

Results

Patient demographics. The final cohort had a mean age of 65 years (35 to 93), and there were 48 (57.1%) males and 36 (42.9%) females. In all, 45 patients (53.6%) had medical comorbidities that could increase their risk of infection (diabetes, peripheral vascular disease, rheumatological conditions, vascular disease, renal failure, hepatic failure, or chronic pulmonary disease).[22] The mean follow-up time from date of last surgical intervention to last recorded follow-up or patient death (n = 12) was 4.74 years (4 months to 14 years).

Isolated organisms. A total of 71 patients (84.5%) had an identified organism cultured from their first stage, compared to 36 patients (48.9%) following their second stage (p < 0.001, chi-squared test). Figure 2 shows the specific micro-organisms isolated from both first- and second-stage intraoperative samples.

Of the 36 patients who had an identifiable organism from their second stage samples, 29 (80.5%) had a change in organism, compared to seven patients who had the same isolated organism at first and second stage.

Treatment outcome. Overall, 50 patients (59.5%) had successful eradication of their PJI following their two-stage revision, requiring no further surgical intervention or antimicrobial suppression compared to 34 (40.5%) patients who had recurrence of infection – either clinically or microbiologically – and who underwent further surgical or non-surgical treatment. Figure 3 shows the outcome of the complete patient cohort using the Musculoskeletal Infection Society (MSIS) outcome tier system.[23]

Table I shows the patients' demographics and microbiology results at the first and second stages with regard to their treatment outcome. In the infection eradication cohort, there were nine patients who were culture negative from both the first and second samples, and two patients in the infection recurrence cohort. Excluding those patients who were culture negative for both the first- and second-stage samples (n = 9) in the infection eradication cohort, and two patients in the infection

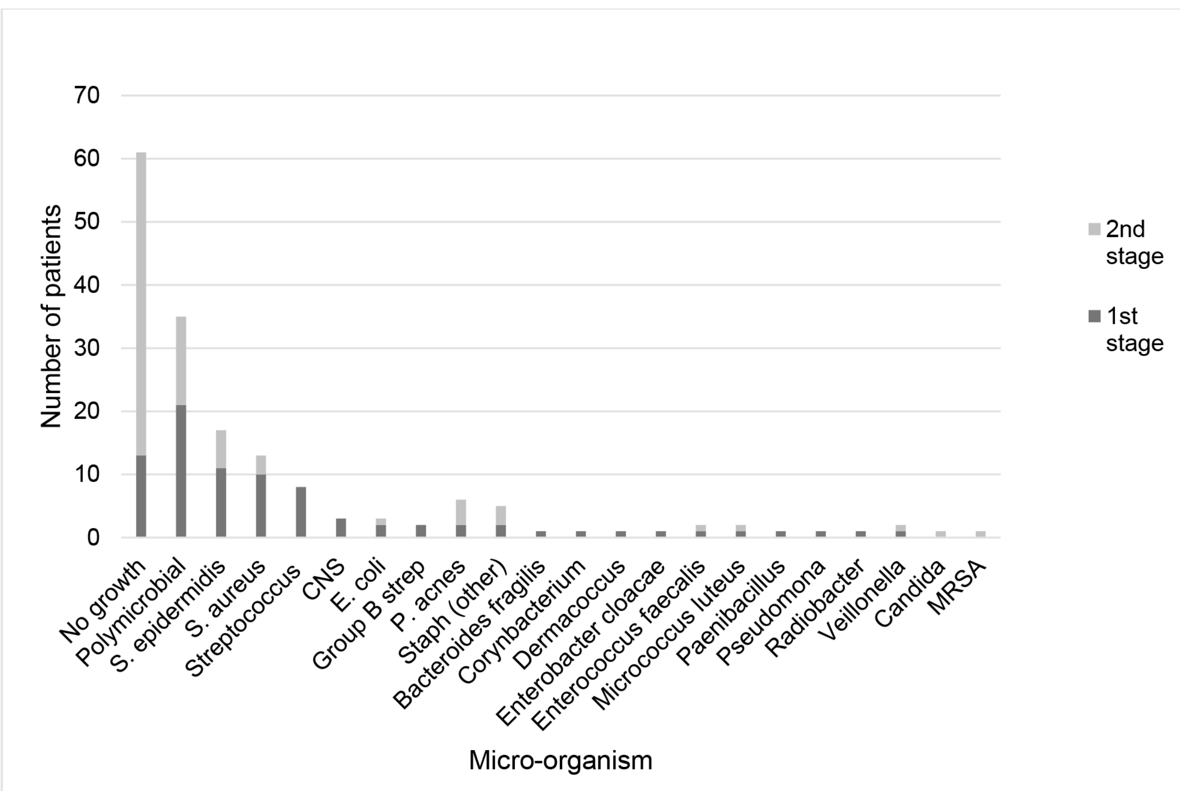

Fig. 2

Isolated micro-organisms at first and second stage revision surgeries.

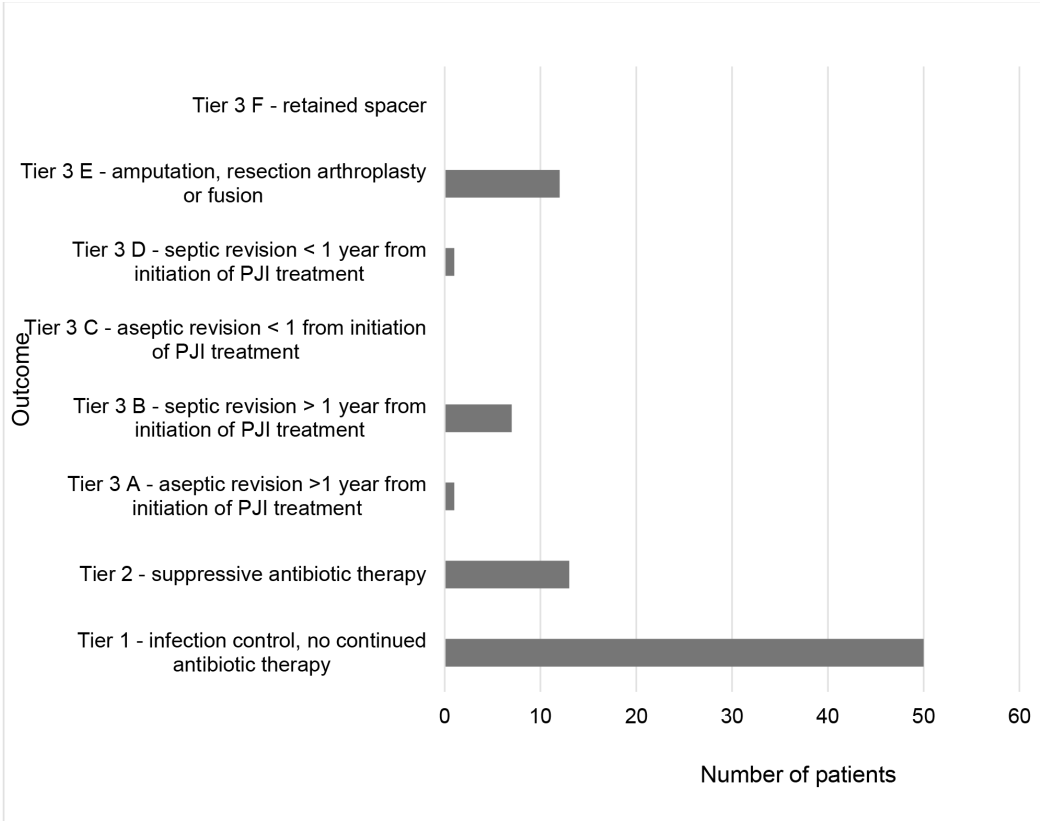

Fig. 3

Outcome following two-stage total knee arthroplasty revision.

recurrence cohort) in the infection eradication cohort, there were nine patients (21.9%) who had a change in the causative organism. In the infection recurrence cohort, there were 20 patients (62.5%) who had a change in their causative organism (p = < 0.01, chi-squared test). Growth at the second stage (n = 36) was associated with a significantly increased risk of failure of treatment (odds ratio (OR) 5.95, 95% confidence interval (CI) 2.29 to 15.49; p < 0.001, chi-squared test), with 13 patients (26%) having a positive growth in the eradication group, and 23 patients (67%) having a positive growth in the failure group. When adjusting for confounding on regression analysis ($R^2 = 0.26$), there was no association when the identified organism at the second stage was the same as the first stage (OR 2.50, 95% CI 0.49 to 12.50; p = 0.269, chi-squared test). However, when a different organism was identified at the second stage, this was independently associated with failure of treatment (OR 8.40, 95% CI 2.91 to 24.39; p < 0.001, chi-squared test).

Further intervention. Figure 4 shows the further treatment given to the 34 patients who had failure of their two-stage revisions. There was no statistical difference between the two cohorts for any of the treatment options.

Discussion

This retrospective two-centre cohort study of 84 patients was conducted to assess the outcome following two-stage TKA revision surgery, in particular the influence of the micro-organisms isolated during the first and second stages. An overall eradication of infection rate of 59.5% was reported following two-stage revision surgery. The most notable finding was that the number of cases with a change in isolated micro-organisms between the first and second stages was the only significant difference between the cohorts. The effect of change in organism between stages has been assessed in previous studies; however, in contrast to the current study, they consist of smaller cohorts and/or from single centres.

There are limitations to the current study. The mean follow-up of the current study's cohort was 4.74 years, but with some patients received follow-up of less than a year. These cases, however, included those who had had a salvage procedure, such as an amputation; therefore, longer-term follow-up to ensure eradication of the infection was not required. The definition of PJI for the current study was a documentation in the medical records from the treating surgeon, based on a combination of clinical diagnosis, serological markers, and radiological features. An alternative gold standard for PJI diagnosis

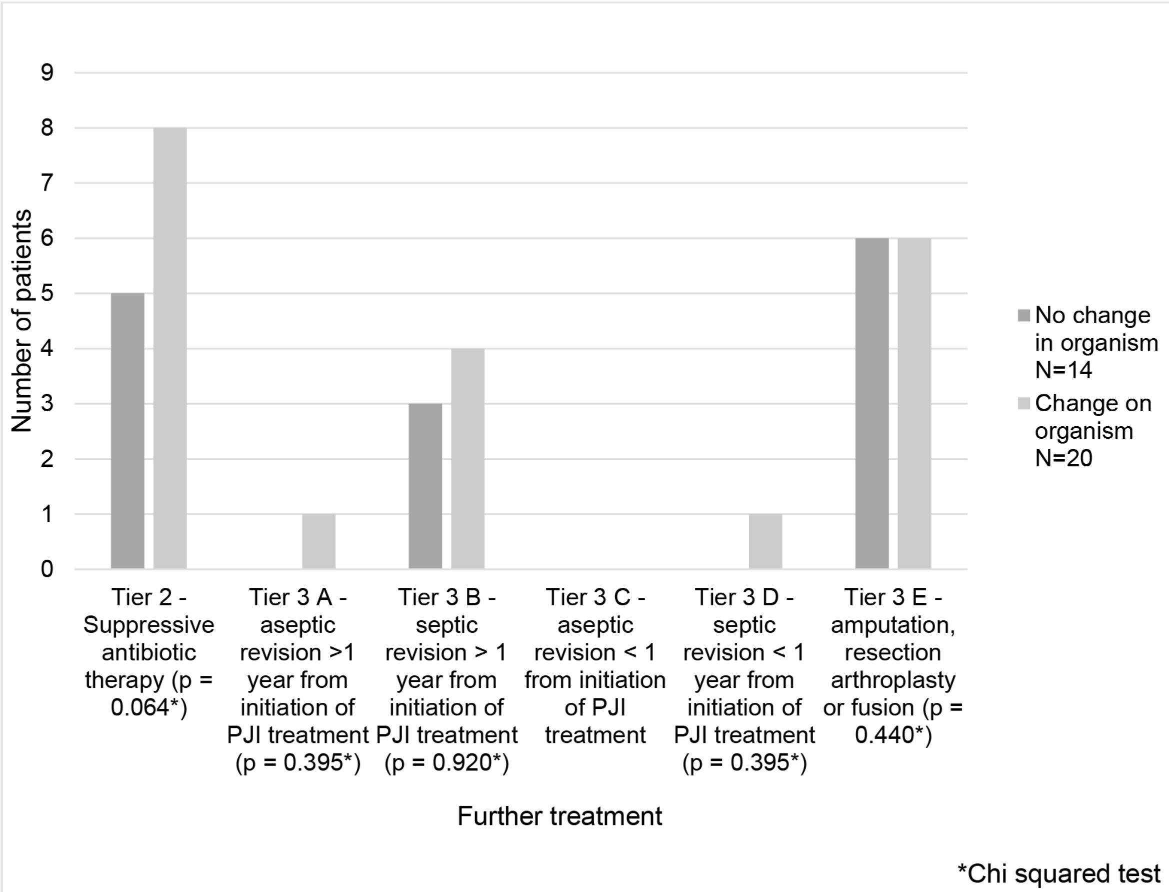

Fig. 4

Ongoing patient treatment following infection recurrence after two-stage total knee arthroplasty revision.

is the internationally accepted diagnostic criteria from the MSIS workgroup;[24] however, this was not used, as the majority of patients did not have all investigations completed to use these criteria. Furthermore, Honkanen et al[25] suggested that true PJI cases could be missed by the MSIS criteria as a result of the exclusion of clinical decision-making. A further potential limitation of the current study was the heterogenicity of surgeons, and therefore potential surgical techniques across the cohort. However, this may make the results more applicable to clinical practice throughout the healthcare system. The current study's cohort size is smaller than that of previous studies in this area;[26-28] however, to the authors' knowledge, the inclusion of more than one centre's data in the analysis is unique factor. Again, this increases the generalizability of the reported findings.

The retrospective design meant that some data collection was lacking, and some patients were excluded as their datasets, particularly the microbiology results, were incomplete. Microbiology results of preoperative aspirations were not included in the final analysis as this information was not available for several patients due to the samples being taken at another hospital before referral on to one of the study centres. Documentation on the use of interim antimicrobials was often lacking, such as the type of antibiotics given, the length of the course, and the route of administration, as well as details of the antibiotics loaded into the cement spacers, so these was not included in the final analysis. There was also variable documentation of the use of intraoperative tourniquet, so despite its previously recorded association with an increased risk of infection,[29] this was not included in the final data set. The retrospective nature design, however, meant that the data recorded in real time was done so without bias and with no influence from the current study.

The current reported clinical success from this cohort is 59%, and is lower than the average reported rate of 80% at ten years.[30] This may be due to the current study's long data collection period of 13 years, or a limitation of the retrospective design, with patients without recurrence of infection potentially being more likely to be lost to follow-up. Another potential influencing factor may be that the most common microbiology result at the first stage was polymicrobial. Bozhkova et al[31] found polymicrobial infections to have a significantly higher

Table I. Comparison of infection eradication and infection recurrence cohorts.

Variable	Infection eradication (n = 50)	Infection recurrence (n = 34)	p-value
Mean patient age, yrs (range)	66.7 (35.4 to 93.4)	64.3 (57.0 to 83.2)	0.179*
Sex, M:F	30:20	18:16	0.521†
Risk factors for infection, Y:N[22]	27:23	18:16	0.923†
Culture positive:culture negative	41:9	32:2	0.106†
Single organism:polymicrobial	27:14	24:8	0.398†
Change in causative organism, Y:N	9:32	20:12	**< 0.001**†

Bold signifies p-value that is statistically significant.
*Independent Student's *t*-test.
†Chi-squared test.

Table II. Summary of literature reviewing two-stage knee revision surgery and isolated organisms at the first and second stages.

Authors	Size of cohort	Single or multicentre	Patients with change in organism, n (%)	Relevance of change in organism
Azzam et al[16]	17	Single	1 (5.8)	No comparison made
Faschingbauer et al[26]	96	Single	N/R	No comparison made
Bejon et al[27]	152	Single	9 (5.9)	No correlation
Akgün et al28	163	Single	18 (11.0)	No comparison made
Hart et al44	48	Single	11 (22.9)	No correlation
Frank et al[45]	52	Single	43 (83.3)	No comparison made
Frank et al[46]	37	Single	31 (83.3)	No comparison made

N/R, not recorded.

rate of failure following two-stage revision compared to monomicrobial infections. Polymicrobial infections also raise the possibility that changes to the specific micro-organisms cultured may not represent a true change in the infective organisms, but that the full spectrum of present micro-organisms was not identified from the samples obtained. In the current study, however, the rate of polymicrobial infections decreased from first to second stage. The presence of micro-organisms was also determined in each case by culturing multiple intraoperative tissue samples which have previously been reported to have improved diagnostic value compared to a single preoperative aspiration.[32] Using open surgical samples rather than percutaneous aspiration samples has also been previously reported to increase the sensitivity of the microbiology results, and reduce the risk of a false-positive result from contamination.[33]

High recurrence rates in PJI with resistant organisms have been reported,[34] and Kim et al[19] reported a higher rate of failure following second two-stage revisions in those patients with methicillin-resistant *Staphylococcus aureus* (MRSA) or fungal infections. However, in the current study, there was only one case of resistant isolates from second-stage samples (MRSA), so these likely had no significant effect on the data analysis. This case had culture-negative samples from the first stage, so was considered a true change in organism for the purpose of data analysis, rather than a change in sensitivities of a previously identified organism.

The current study found no significant difference between patient demographics, including risk factors for infection, between those patients that had failure of their two-stage revision (i.e. recurrence of infection) and those who had successful eradication. This is inconsistent with the findings of Vadiee et al[35] and Matar et al,[36] who found significantly higher rates of failure following two-stage revision in physiologically compromised patients. This may be explained by the overall high comorbid state of the reported cohort of patients (> 50% having risk factors for infection), thereby reducing any difference between the two cohorts. The current study's patient cohort was identified from two tertiary hospitals based in the north of the UK, an area known to have a morbidity.[37] The high rate of morbidity in the current study is also consistent with polymicrobial growth being more common than a single isolate at both first and second stages. Increased age,[38] higher American Society of Anesthesiologists grade,[39] and obesity[40] have been shown to be associated with polymicrobial PJIs potentially.

Having culture-positive or culture-negative sampling at reimplantation was found not to have an effect on outcome following two-stage revision in the current study, which reported a positive culture rate at second stage of 48.9%. The finding is consistent with the reported outcomes from Kim et al,[20] who found that the culture outcome had no effect on the overall outcome of the two-stage revision; however, culture-positive cases were significantly more likely to undergo reoperation between the initial first and second stages. The current study's rate of positive cultures at reimplantation is higher than that previously reported,[41] and may be related to the comorbid patient cohort.[37] Pre-reimplantation aspirations are not routinely performed at the current study's centre. While this may have identified more positive cultures cases and deferred the second stage, the use of an aspiration with an antibiotic cement spacer in situ has been previously reported to be of limited value.[42] Furthermore, Cordero-Ampuero et al[43] have reported only 21% of culture-positive cases at reimplantation, translated into recurrence of infection defined by symptoms, radiological, and serological markers.

Azzam et al[16] reviewed reinfection following two-stage revision and found a change in causative organism in only one of their 17 patients. There was no comparison made between a cohort of successful two-stage revision patients. Faschingbauer et al[26] found no difference in infection recurrence rates between difference causative organism groups following two-stage revision in a cohort of 96 patients, but they did not look specifically, and the influence of change in organism group between the two stages. Hart et al[44] found 11 (29%) positive cultures at reimplantation in a cohort of 48 patients, with seven cases having a change in organism, but no correlation was found between culture results and treatment outcome. Similarly, Bejon et al[27] analyzed a cohort of 152 patients from a single centre reported a change in pathogen in 6% of cases, but this had no effect on treatment outcome.

There was also no evidence from Bejon et al[27] that positive reimplantation cultures were associated with worse outcome, but more antibiotics were given to those patients. Akgün et al[28] however, found a significantly higher rate of failure in patients with positive cultures at reimplantation in their single-centre study. Furthermore, they also reported that the same organism was identified at the first and second stages in 33.3% of patients, but there was no statistical analysis regarding the influence of this finding on outcome.[28] Frank et al[45] reported on high rates of a change in cultured organisms between explantation and spacer exchange, as well as first- and second-stage revision of both hip and knee prosthesis;[46] again, however, the influence of change of causative organism was not specifically commented on. A summary of the pre-existing literature is shown in Table II.

A systematic review by Maden et al[47] concluded that while all surgical techniques for managing failed two-stage revisions had high complication rates, knee arthrodesis had a lower risk of failure than a repeat two-stage revision. However, there were only nine studies available for inclusion in this review. The current study showed no significant difference in treatment following failure of two-stage revision for those patients, with or without a change in causative organism. A larger multicentre study may help determine the most appropriate treatment strategy, taking into account the potential effect of a change in organism.

In conclusion, the current study reports that a change in isolated organism between the first- and second-stage revision for deep infection of TKA was independently associated with an increased risk of failure. To the authors knowledge, this is a novel finding, and has the potential to influence postoperative monitoring and management of these patients. Aspiration or biopsy prior to the second stage for culture may help direct treatment decisions and target antibiotic management.

Take home message

- The current study reports that a change in isolated organism between the first- and second -stage revision for deep infection of total knee arthroplasty was independently associated with an increased risk of failure.
- Aspiration or biopsy prior to the second stage for culture may help direct treatment decisions and target antibiotic management.

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