■ ARTHROPLASTY

Two-stage revision for periprosthetic joint infection after hip and knee arthroplasty

THE ROLE OF REIMPLANTATION HISTOLOGY IN REINFECTION RATE

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Aims

Histology is widely used for diagnosis of persistent infection during reimplantation in two-stage revision hip and knee arthroplasty, although data on its utility remain scarce. Therefore, this study aims to assess the predictive value of permanent sections at reimplantation in relation to reinfection risk, and to compare results of permanent and frozen sections.

Methods

We retrospectively collected data from 226 patients (90 hips, 136 knees) with periprosthetic joint infection who underwent two-stage revision between August 2011 and September 2021, with a minimum follow-up of one year. Histology was assessed via the SLIM classification. First, we analyzed whether patients with positive permanent sections at reimplantation had higher reinfection rates than patients with negative histology. Further, we compared permanent and frozen section results, and assessed the influence of anatomical regions (knee versus hip), low- versus high-grade infections, as well as first revision versus multiple prior revisions on the histological result at reimplantation. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), chi-squared tests, and Kaplan-Meier estimates were calculated.

Results

Overall, the reinfection rate was 18%. A total of 14 out of 82 patients (17%) with positive permanent sections at reimplantation experienced reinfection, compared to 26 of 144 patients (18%) with negative results (p = 0.996). Neither permanent sections nor fresh frozen sections were significantly associated with reinfection, with a sensitivity of 0.35, specificity of 0.63, PPV of 0.17, NPV of 0.81, and accuracy of 58%. Histology was not significantly associated with reinfection or survival time for any of the analyzed sub-groups. Permanent and frozen section results were in agreement for 91% of cases.

Conclusion

Permanent and fresh frozen sections at reimplantation in two-stage revision do not serve as a reliable predictor for reinfection.

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Introduction

Periprosthetic joint infection (PJI) after total joint replacement (TJR) is associated with considerable patient morbidity and mortality.[1] There is a rising rate of primary TJR, which will in turn further increase the number of PJIs.[2,3] Two-stage exchange is considered the gold-standard strategy in the treatment of PJIs with reported success rates up to 90%. Alternative strategies are one-stage exchange, debridement antibiotics and implant retention (DAIR), or three-stage revision, which is typically used in cases of fungal infections.[4-8]

Recently, there have been numerous attempts to improve the diagnosis of persistent infection prior to the second stage of revision. However, despite a variety of serological and synovial fluid markers investigated before and during reimplantation, there is no consensus on the most effective tests.[9] ESR, CRP,[10] synovial fluid culture, synovial neutrophil percentage,[9] serum white blood

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Table I. Comparison of demographic variables between histology groups.

Variable	Negative histology	Positive histology	p-value
Cases, n	144	82	
Male sex, n (%)	66 (46)	41 (50)	0.642*
Median age, yrs (IQR)	72 (64 to 77)	71 (61 to 79)	0.550†
Median BMI, kg/m² (IQR)	27.6 (23.4 to 31.2)	28.1 (24.3 to 32.3)	0.331†
Diabetes, n (%)	39 (27)	27 (33)	0.437*
Median CCI (IQR)	4 (3 to 5)	4 (2 to 5)	0.491*
Joint, n (%)			0.421*
Knee	90 (63)	46 (56)	
Hip	54 (38)	36 (35)	

*Chi-squared test.
†Wilcoxon signed-rank test.
CCI, Charlson Comorbidity Index; IQR, interquartile range.

Table II. Predictive properties of permanent sections at reimplantation compared between joints.

Variable	TKA (n = 136)	THA (n = 90)
Sensitivity, % (95% CI)	36 (19 to 55)	33 (8 to 70)
Specificity (95% CI)	67 (57 to 77)	59 (48 to 70)
PPV, % (95% CI)	24 (15 to 35)	8 (3 to 19)
NPV, % (95% CI)	78 (72 to 82)	89 (83 to 93)
Accuracy, % (95% CI)	60 (51 to 68)	57 (46 to 67)

NPV, negative predictive value; PPV, positive predictive value; THA, total hip arthroplasty; TKA, total knee arthroplasty.

cell (WBC) count,[11] and synovial WBC count[12] have so far only shown moderate sensitivity and specificity in identifying patients at risk of persistent infection and therefore at high risk of revision failure.[9,13]

Histological samples are routinely collected during reimplantation to provide a more comprehensive assessment of revision failure risk due to persistent infection.[13] Histology plays an essential role in the diagnostic evaluation of PJIs at the time of explantation, according to the Musculoskeletal Infection Society (MSIS) and European Bone and Joint Infection Society (EBJIS) criteria.[14,15] However, there is limited evidence on their utility during the second stage of revision. Neither before nor after the standardization of histological analysis through the SLIM consensus classification have studies or consensus statements produced clear evidence on the clinical relevance of positive histology at reimplantation.[14-17] Current research has so far focused on frozen sections and MSIS criteria at reimplantation, revealing low sensitivity for both.[13,16-18]

The aim of this study was to evaluate the diagnostic performance of permanent sections at reimplantation in two-stage exchange total knee (TKA) or total hip arthroplasty (THA) to predict repeated failure due to reinfection. Further, we aimed to identify factors associated with positive permanent sections at the second stage of revision, and to compare frozen to permanent section results.

Methods

This study was approved by the local ethics committee (Nr.1259/2021). Informed consent was not required for this retrospective data analysis.

Records from patients who underwent two-stage revision for PJI after TKA or THA at our institution between August 2011 and September 2021 were retrospectively reviewed. Our workup included preoperative blood samples to assess inflammatory parameters, joint aspiration with analysis of synovial fluid for WBC count, percentage of polymorphonuclear neutrophils, and microbiological investigations. Intraoperatively, three to six samples were sent for microbiological and histopathological analysis. Cultures were held for 14 days.

MSIS criteria, and later the 2018 consensus criteria, were used to diagnose PJI and recurrent PJI after reimplantation, and reinfections were included in this study if they were classified as tier 3B or tier 3D according to the MSIS 2019 consensus statement (Supplementary Table i).[18,19] The minimum follow-up duration was one year after reimplantation, and patients were excluded if two-stage revision failed for reasons other than reinfection, or due to missing data.

Patients routinely received spacers with vancomycin and gentamicin cement, usually lasting six to eight weeks. Antibiotics were administered according to a standard regimen, starting with two weeks of intravenous antibiotics after explantation, followed by four weeks of oral antibiotics depending on the respective antibiogram and the recommendations of our infectious disease specialists until reimplantation. After the second stage, the antibiotics were continued intravenously for another two weeks with additional antibiofilm active drugs (fosfomycin or rifampicin) for one week, followed by four to ten weeks of oral antibiotics. The administration of antibiotics between stages, as well as after reimplantation, was performed in line with the long-interval antibiotics concept.[20,21]

At reimplantation, five representative samples were obtained from the respective knee (tibia, femur, dorsal joint capsule, and synovial samples) or hip (femur, acetabulum, and synovial samples) depending on the assessment of the operating surgeon. Permanent sections were assessed by four specifically trained pathologists (LK, see Acknowledgements), using the SLIM consensus classification at the time of reimplantation; pathologists were thus unaware of the respective outcome at the time of analysis.[16] SLIM I (particle induced) and SLIM IV (indifferent) were classified as negative histology, whereas SLIM II (infectious) and SLIM III (combination of particle-induced and infectious) were rated as positive histology. Positive results were further divided into high-grade and low-grade infections,[22] with a cutoff of 23 neutrophilic granulocytes per ten high-power fields.[23] We additionally collected data on frozen sections at reimplantation, which were also assessed using the SLIM classification, bacteriological findings at explantation, and the number of previous revision surgeries. *Staphylococcus aureus*, coagulase-negative staphylococcus, fungal infections, enterococcus, streptococcus, pseudomonas, and multi-organism infections were considered high-virulence, while *Staphylococcus epidermidis*, *corynebacterium*, *Escherichia coli*, enterobacter, propionibacterium, and *proteus mirabilis* were considered low-virulence.[24]

In addition, demographic data on age at reimplantation, sex, BMI, and diabetes were obtained. The Charlson Comorbidity Index (CCI) was used to summarize comorbidities.[25]

Statistical analysis. Demographic variables were analyzed descriptively via median and quartile values for metric variables,

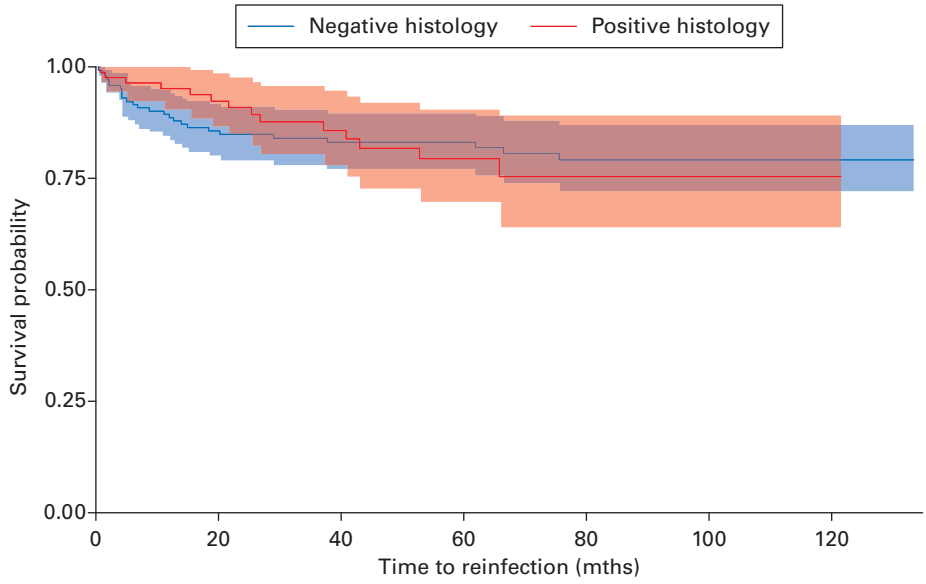

Fig. 1

Kaplan-Meier estimation of patients with negative versus patients with positive histology at reimplantation.

and absolute numbers in combination with percentages for categorical variables. Depending on the respective distribution, groups were compared via independent-samples *t*-tests or Wilcoxon signed-rank tests. A chi-squared test was applied for categorical variables, or a Fisher's exact test for fewer than five observations. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and relative risk were calculated for contingency tables of dichotomous variables. Kaplan-Meier curves were calculated and further analyzed through log-rank testing. All tests were performed in their two-sided versions at a significance level of 0.05 using R v. 4.2.2 (R Foundation for Statistical Computing, Austria).

Results

Demographic data. From 248 initially identified cases, 17 were excluded due to revision failure for reasons other than reinfection, and five due to missing histological data. The remaining 226 records were used for further analysis, including 136 TKA and 90 THA revisions. The median follow-up duration was 50.3 months (interquartile range (IQR) 20.8 to 90.4). Positive histology at explantation was given in 212 cases (94%). There was no association between revision failure and sex ($p = 0.214$, chi squared test), diabetes ($p = 0.754$, chi squared test), or CCI ($p = 0.197$, chi squared test), whereas patients suffering from reinfection were significantly younger ($p < 0.001$, Wilcoxon-test) and had a higher BMI ($p = 0.036$, Wilcoxon-test).

Histology at reimplantation and reinfection. Positive permanent sections at reimplantation were present in 82 (36%) of the cases. No significant differences with regard to sex, age at revision, BMI, diabetes, CCI, or implant location were found between patients with positive and negative histology at reimplantation (Table I).

Overall, reinfection occurred in 40 (18%) two-stage revisions. In total, 14 of 82 (17%) patients with positive histology at reimplantation suffered reinfection, compared to 26 of 144 (18%) patients with negative histology ($p = 0.996$, chi squared test), resulting in a sensitivity of 0.35, specificity of 0.63, PPV of 0.17, NPV of 0.82, accuracy of 58%, and relative risk of 0.95. Kaplan-Meier survival estimates between positive and negative histology groups are given in Figure 1, and did not significantly differ between groups ($p = 0.999$, log rank test). Of these 40 infections, 20 (50%) occurred within the first year of reimplantation, four (20%) of which had positive histological findings at reimplantation.

Frozen versus permanent sections. We were able to obtain additional frozen section results for 194 patients.

Positive frozen section results were not signifficantly associated with a higher risk of reinfection ($p = 0.569$, chi squared test). We found a sensitivity of 0.29, specificity of 0.76, PPV of 0.22, and NPV of 0.82. In 177 cases (91%), the frozen and permanent section results were consistent.

A total of 48 frozen sections (25%) were indicative of inflammation. Of these, 47 (98%) cases had positive permanent section results, while only one case (2%) had a negative permanent section result. Among the 146 (75%) cases with negative frozen sections, 16 (11%) subsequently had positive permanent sections, 130 (89%) cases had negative ones, and 26 (18%) suffered reinfection.

High versus low grade at reimplantation. For 67 out of 82 patients with positive histology at reimplantation (82%), findings were classified as low-grade infection, whereas in 15 cases (18%) a high-grade infection was detected. With a reinfection rate of 16% for low- and 20% for high-grade cases, there was no significant difference found between the two groups ($p = 0.714$, chi-squared test).

TKA versus THA. Overall, 31 of 136 (23%) TKA patients had a revision failure, as opposed to nine out of 90 (10%) THA patients. Positive histology was found in 46 of 136 (34%) TKA

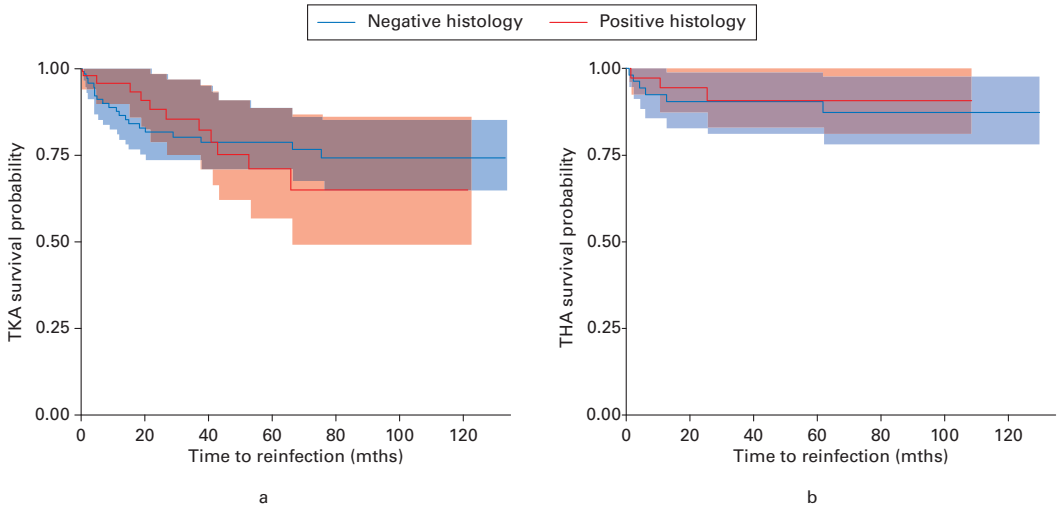

Fig. 2

Kaplan-Meier estimates of total knee arthroplasty (TKA) and total hip arthroplasty (THA) survival grouped into negative and positive histology, respectively.

revisions and 36 of 90 (40%) THA revisions (p = 0.421, chi-squared test), and was not associated with failure for reinfection in either of the two groups (p = 0.995 for TKA, chi-squared test; p = 0.736 for THA, Fisher's exact test). Reinfection rates significantly differed between the hip and knee cohort (p = 0.022, chi-squared test), as did Kaplan-Meier survival estimates (p = 0.018, log rank test, Table II, Figure 2).

First revision vs multiple revisions. For 122 patients (54.0%) it was their first revision, whereas 104 patients (46.0%) had already undergone at least one prior revision. Repeated revisions were not associated with a higher rate of positive permanent sections (p = 0.186, chi-squared test), but were significantly linked to higher reinfection rates (p = 0.033, chi-squared test) and shorter implant survival (p = 0.031, log-rank test, Figure 3).

Bacterial cultures. Positive cultures were found in 166 of 226 cases at explantation (74%), and in 31 of 226 cases at reimplantation (14%). Positive cultures did not correlate with positive histology at reimplantation (p = 0.764, chi-squared test), with a sensitivity of 32%, specificity of 63%, PPV of 12%, NPV of 85%, and accuracy of 59%. In 26 cases (12%), more than one pathogen was detected at explantation, but there was no correlation with positive histology at reimplantation (p = 0.589, chi-squared test). Positive cultures at reimplantation did not correlate with failure (p = 0.999, chi-squared test), with a sensitivity of 13%, specificity of 86%, and accuracy of 73%.

High-virulence pathogens were detected in 83 of 166 bacterial cultures (50%), but were not significantly correlated with positive histology at reimplantation (p = 0.871, chi-squared test) or failure for reinfection (p = 0.683, chi-squared test). An overview of pathogens at explantation is given in Figure 4.

Discussion

Diagnosis of persistent infection in two-stage revision arthroplasty remains a major challenge despite a multitude of pre- and intraoperative serological, synovial, or histological tests.[10,12,13,26] Fresh frozen and permanent sections are therefore commonly used to further assess infection eradication at time of reimplantation, despite limited evidence on the validity of this approach.[17,27,28]

This study evaluates the largest patient cohort with both permanent and frozen sections at reimplantation in two-stage TKA/THA revision in the literature; the closest comparable study includes 97 patients.[9] We demonstrated that neither permanent nor frozen section results can successfully predict the risk for reinfection after two-stage revision, which further underlines the findings of the 2018 International Consensus, stating that frozen sections suffer from low sensitivity at time of reimplantation.[17] Thus, positive histology joins the list of markers inadequate to assess infection persistence at the second stage of revision, such as ESR, CRP, serum WBC count, synovial WBC count, and gram stains.[9,10,12,13] Identifying patients who will suffer reinfection based on information at reimplantation remains a major challenge, even if a combination of tests is used. Similar to one-stage revision, which has shown almost equivalent success rates in selected cases,[4-7] infection control may depend more on the accuracy and radicality of the debridement than on the presence of infection-related histological changes, or the levels of serum and synovial markers.

Further, our results might help to explain why the MSIS criteria, which are partly based on histological findings, have so far not proven useful at the second stage of revision due to low sensitivity.[17,27,29,30] Additionally, established cutoffs for various markers used in initial PJI diagnosis may need further reassessment and adjustment to maintain validity at time of reimplantation.

Multiple studies have found agreement between frozen and permanent sections of over 90% for both hip and knee joints.[31] Even in the case of contradictory results, no effects on prosthesis survival after staged revision have been demonstrated.[14,15] Our findings align with previous results, showing a 91% agreement

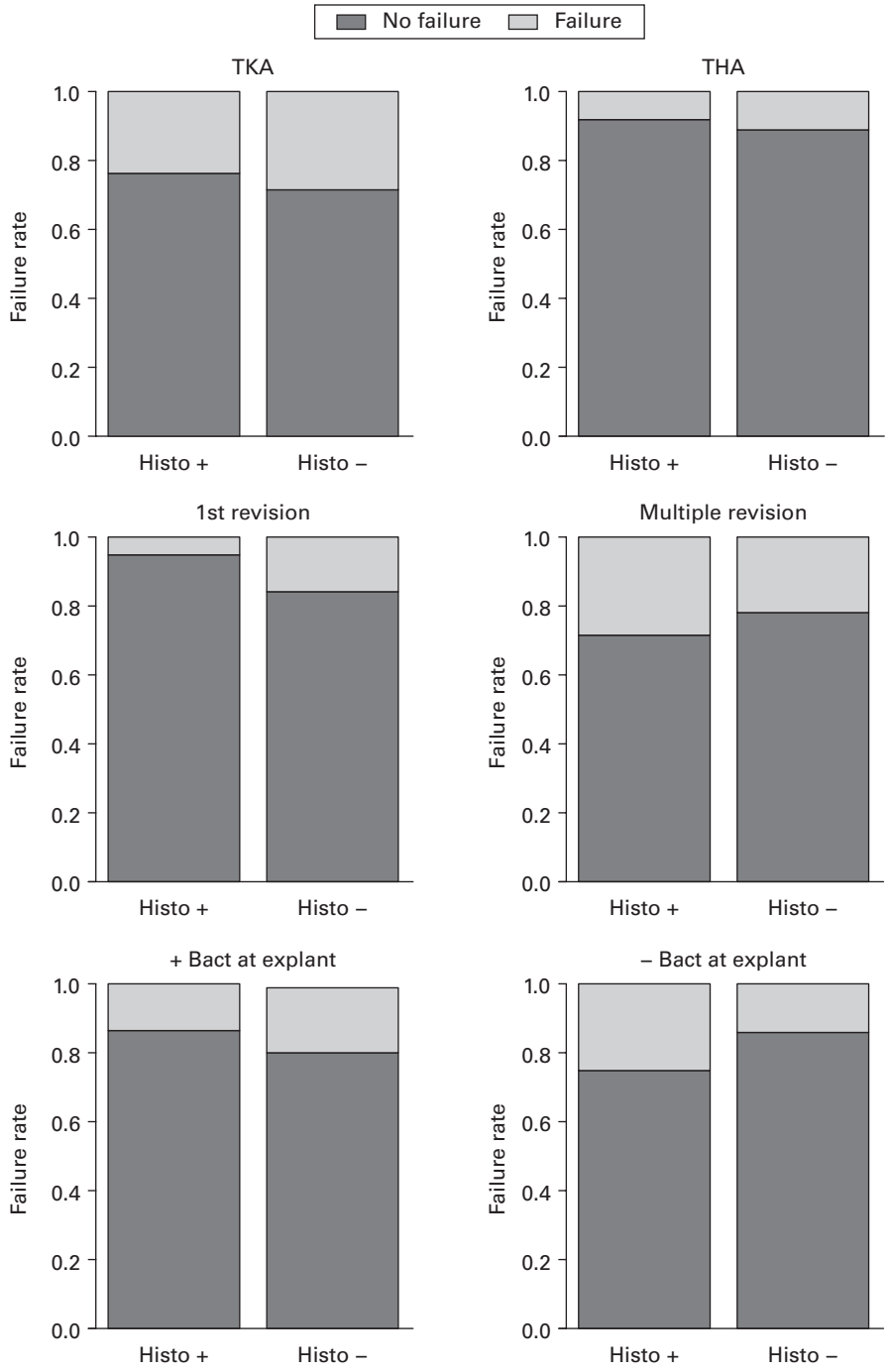

Fig. 3

Comparison of failure rates between groups, depending on positive (Histo +) or negative (Histo -) histology at reimplantation. THA, total hip arthroplasty; TKA, total knee arthroplasty. Bact, bacteria.

between both methods. With only a minimal gain in sensitivity compared to frozen sections, limited predictive power, and the availability of results only postoperatively, it is questionable whether the analysis of permanent sections is necessary in view of current evidence.

We found a marked reduction in histological findings indicative of infection between the first and second stage of revision, as only 36% of the cases in our study presented with SLIM type II or III at reimplantation, compared to approximately 60% at explantation reported by other authors and 94% in our cohort.[15,22]

Overall, 18% of type II or III samples were classified as high-grade infection with more than 23 neutrophilic granulocytes per ten high-power fields. However, failure rates for reinfection

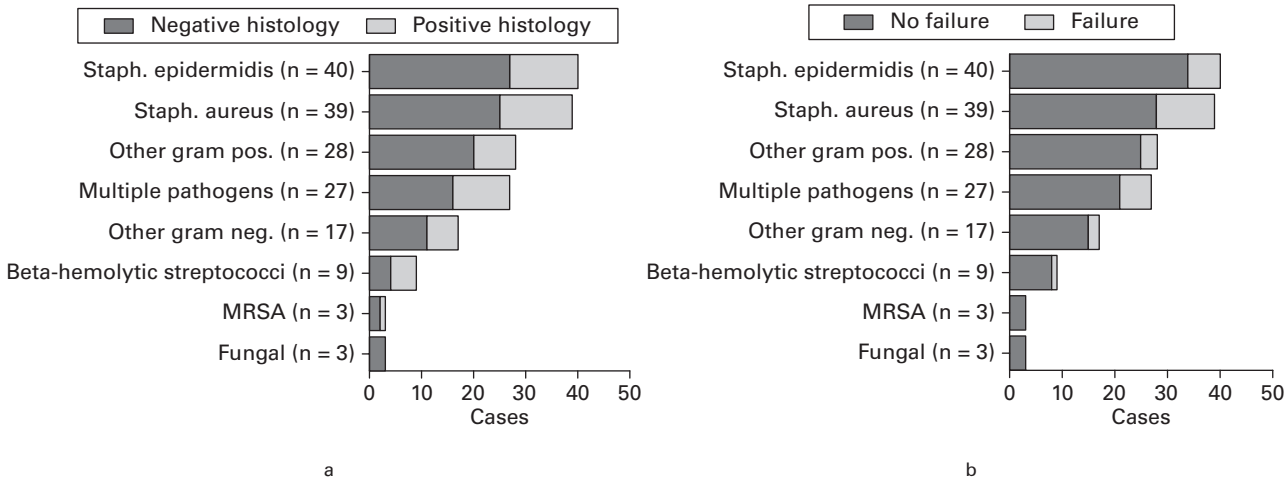

Fig. 4

a) Histological results at reimplantation categorized by pathogen groups, and b) failure rates based on the respective pathogen types. Pathogens considered as highly virulent are printed in bold. MRSA, methicillin-resistant *Staphylococcus aureus*.

were almost equal between low- and high-grade cases. Further, Munemoto et al[32] reported the sporadic presence of neutrophilic granulocytes, which serve as a basis for the SLIM classification system, for 43% of patients at the second stage of hip revision despite negative culture results and no clinical findings indicative of persistent infection.[16] This too raises the question of whether other cutoffs are needed for reimplantation.

A possibility to compensate for the lack of predictive power of permanent sections at reimplantation lies within the refinement of the SLIM consensus classification. An extension of the existing system to include type IX A and type IX B was proposed for evaluation in the second revision step. It involves the quantification of granulocytes and the CD15 focus score, which comprises the immunohistochemical detection of CD-15-positive neutrophil granulocytes.[22,33] However, further studies are needed to evaluate the added diagnostic and prognostic value of the newly proposed classification categories before including them in clinical practice.

Our results are comparable with current literature in terms of pathogen detection rates and microbiological spectrum, with 74% positive and 11% polymicrobial cultures at explantation.[34,35] There was no significant association between positive histology at reimplantation and microbiological pathogen detection. A clear tendency towards lower sensitivity and only moderate specificity with regard to culture results at the second stage of revision was demonstrated, compared to what was previously found at the first stage of revision.[36] Permanent sections were therefore unreliable to rule out positive culture results, contrary to previous evidence showing that microbiology is associated with reinfection after reimplantation.[34]

Success rates in staged revision currently range from 78% to 95% in knees[37,38] and 70% to 95% in hips,[39] when no prior revisions for infection had been performed. In the case of repeated revisions, reinfection rates rise up to 49% for knees and 43% for hips.[40,41] We found reinfection rates after two-stage revision to be more than twice as high in knees (23%) compared to hips (10%), which is comparable with current literature.[42] However, the difference in positive histology rates between knee and hip joints was negligibly small, and almost identical sensitivity and specificity was found in both groups. Differences regarding PPV may be attributed to the lower number of patients in the hip cohort, or differences in histological sampling techniques. George et al[27] reported considerably higher sensitivity and area under the receiver operating characteristic curve for permanent sections in hip compared to knee joints when matched with MSIS criteria at reimplantation, but these differences were primarily due to the comparably small cohort of 38 knees and 41 hips. Other authors have advised separate histological analysis of knee and hip joints,[15] but there is a lack of evidence on whether or not different inflammatory responses between joints or sampling techniques cause considerable differences in histological analysis.[42]

This study has several limitations. First, its retrospective design and reduced sample size are subject to associated biases common to these studies, while our single-centre approach further limits generalizability. Second, histological analysis depends on the respective pathologists, and is prone to biases that could be overcome through blinded analysis. Third, the acquisition of samples is surgeon-dependent, which potentially influences histological sample quality, and therefore the accuracy of our analysis. Fourth, due to the extended follow-up duration, a haematogenous cause of reinfection cannot be excluded as a reason for reinfection with utmost certainty.

In conclusion, we demonstrated that permanent section results at reimplantation in two-stage revision have a high agreement with frozen section results, and provide no added value for estimating reinfection risk. We found low sensitivity and specificity, despite analyses being conducted by specifically trained pathologists. In view of current evidence, our findings do not support the continued use of permanent sections at reimplantation. Further studies are needed to identify optimal combinations of suitable diagnostic and prognostic markers at the second stage of revision hip and knee arthroplasty.

Take home message

- Histological analysis at reimplantation cannot reliably predict reinfection risk in two-stage revision hip or knee arthroplasty.
- There is great agreement between frozen section and permanent section results at second stage, however both show limited sensitivity, specificity, and positive predictive and negative predictive values with regard to failure risk.
- Positive histological results at reimplantation are not associated with positive microbiological cultures at reimplantation.

Supplementary material

Treatment outcomes classified according to the Musculoskeletal Infection Society periprosthetic joint infection reporting system.

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