



■ ANNOTATION

Two-stage revision for the culture-negative infected total hip arthroplasty

A COMPARATIVE STUDY

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Aims

Periprosthetic joint infection (PJI) remains a challenging complication following total hip arthroplasty (THA). It is associated with high levels of morbidity, mortality and expense. Guidelines and protocols exist for the management of culture-positive patients. Managing culture-negative patients with a PJI poses a greater challenge to surgeons and the wider multidisciplinary team as clear guidance is lacking.

Patients and Methods

We aimed to compare the outcomes of treatment for 50 consecutive culture-negative and 50 consecutive culture-positive patients who underwent two-stage revision THA for chronic infection with a minimum follow-up of five years.

Results

There was no significant difference in the outcomes between the two groups of patients, with a similar rate of re-infection of 6%, five years post-operatively. Culture-negative PJIs were associated with older age, smoking, referral from elsewhere and pre-operative antibiotic treatment. The samples in the culture-negative patients were negative before the first stage (aspiration), during the first-stage (implant removal) and second-stage procedures (re-implantation).

Conclusion

Adherence to strict protocols for selecting and treating culture-negative patients with a PJI using the same two-stage revision approach that we employ for complex culture-positive PJIs is important in order to achieve control of the infection in this difficult group of patients.

Cite this article: *Bone Joint J* 2018;(1 Supple A)100-B:3–8.

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©2018 Author(s) et al
doi:10.1302/0301-620X.100B1.
BJJ-2017-0626.R1 \$2.00

Bone Joint J
2018;(1 Supple A):3–8.

The United Kingdom's National Joint Registry (NJR) has recorded almost 800 000 primary total hip arthroplasties (THA) since 2003.¹ Of these, 20 926 were revisions and 2889 as a consequence to periprosthetic joint infection (PJI),¹ which can be a catastrophic complication.² This may be an underestimate of the true burden.^{3,4} An increase in the number of revision cases is associated with increased costs to the National Health Service¹ with far greater costs than are anticipated, or funded, for infected cases.⁵

Treating infection involves identifying the organism and administering the appropriate antibiotics. Clear guidance and protocols are available for the management of culture-positive patients.⁶ Culture-negative PJI, however, remains a challenging condition to manage, lacking guidelines or protocols. These cases account for between 5% and 12 % of all PJIs^{7,8} and have variable outcomes.

These patients are usually frail, with many comorbidities, soft tissue problems, communicating sinuses (tracts communicating from skin to prosthesis) and bone loss. Two-stage revision arthroplasty is the most commonly undertaken form of treatment, being more effective than a single-stage revision.^{9,10} Single-stage procedures are contraindicated in culture-negative patients due to a lack of identified organism.¹¹

It has been suggested that the characteristic patient with a culture-negative PJI is a man aged > 65 years with many comorbidities and a body mass index (BMI) of > 25 kg/m².⁷ However, the literature lacks specific analysis of the associated risk factors. This study aims to compare outcomes between culture-negative and culture-positive PJIs in a prospectively compiled database of two-stage revision arthroplasties, identifying the risk factors in these patients.

Table I. Definition of culture-negative periprosthetic joint infection (Berbari et al)⁸

(i) Periprosthetic purulence observed at the time of operation
(ii) Histopathological features consistent with acute inflammation
(iii) Elevated synovial white cell count ($> 1.7 \times 10^3 / \mu\text{L}^3$) or elevated synovial neutrophil (PMN) percentage ($> 65\%$ PMNs) or
(iv) Sinus track in direct communication with the joint

Table II. Contraindications for single-stage revision

Local factors
Significant tissue compromise
Significant bone loss
Peripheral vascular disease
Host factors
Immunosuppression
Concurrent sepsis
Systemic disease
Reinfection
Organism factors
Multi-resistant organisms
Polymicrobial infection
Commensals
Unusual resistance profiles

Table III. Positive diagnostic criteria identified in the culture-negative group

Criteria	Patients (n)
Sinus	2
Histopathology (showing inflammation)	28
Periprosthetic purulence observed at the time of operation	39

Patients and Methods

Consecutive patients who underwent a two-stage revision THA for infection between 2007 and 2012 with a minimum follow-up of five years were recorded from the database. Two groups were identified for this study, those who had negative culture results prior to the first stage procedure and those in whom a specific micro-organism was identified.

Patients with acute PJI (within six weeks of implantation), those with metal-on-metal bearing surfaces and those who underwent a single-stage procedure were excluded.¹²

Routine assessment included a thorough history and examination with blood tests, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white cell count (WCC). The hip was aspirated under fluoroscopic guidance and the fluid was sent to the laboratory for testing. Routine analysis included extended cultures, gram stain, *Coxiella* and *Brucella* serologies, acid-fast bacilli, fungal and sensitivity tests, and polymerase chain reaction (PCR) in a few patients. Sonification of retrieved components is not used routinely in our unit. As part of our protocol, antibiotic treatment is stopped four weeks before the aspiration is undertaken, as described by Oussedik et al¹³ in 2010. Biopsy was also performed to increase sensitivity and accuracy. This should be in combination with aspiration.¹⁴

Patients with a culture-negative PJI were identified at this time, and the diagnosis of PJI in these patients was made based on criteria defined by Berbari et al⁸ in 2007. This includes a failure to isolate micro-organisms following standard aerobic and anaerobic microbiological techniques performed on blood cultures, synovial fluid and samples of periprosthetic tissue and one or more of the criteria listed in Table I.

Patients were separated into single or two-stage treatment regimes according to a standardised protocol for PJIs, based on criteria which have been previously described.¹⁵ Those with contraindications for single-stage revision had two-stage surgery¹³ (Table II).

All procedures were performed by a single surgeon (FSH) in a tertiary centre.

The first stage involves open, aggressive debridement with removal of components and cement. Between three to five tissue samples are taken with separate sterile instruments to limit the risk of contamination¹⁶ and sent for urgent microbiology and histology. Microbiology culture was negative in these samples, but some histology results were positive for inflammation (Table III).

The hip is irrigated with a mixture of hydrogen peroxide and Betadine solutions (Videne, Ecolab Ltd, Swindon, United Kingdom), followed by thorough lavage. The wound is soaked in aqueous Betadine and the edges approximated. The patient is re-draped and the surgical team rescrubs prior to implanting a temporary articulating antibiotic loaded cement spacer with new, clean instruments. The spacer normally contains 3 g vancomycin and 2 g gentamicin per sachet of Palacos R (Heraeus Medical, Wehrheim, Germany), providing broad spectrum cover for organisms commonly encountered with PJIs whilst discouraging the development of resistant strains.¹⁷

The management of all patients is discussed in a multidisciplinary meeting prior to starting specific antibiotics according to a strict protocol.¹⁸ Further discussions follow after obtaining any samples at any stage and the antibiotic programme is changed accordingly. Patients are discharged when they are deemed safe mobilising partially weight-bearing. Following the first stage, all patients usually receive gentamycin and teicoplanin for at least six weeks unless directed otherwise by the multidisciplinary team. They are regularly reviewed to monitor the control of infection, and if there is any doubt about eradication the first stage is repeated until the infection is under control.¹⁸

The decision to proceed to the second stage is determined by the clinical and biochemical response, looking at wound healing and inflammatory and nutritional markers. Once

Table IV. Comparison of variables between culture-negative and culture-positive groups

Variables	Culture -ve group (n = 50)	Culture +ve group (n = 50)
Mean age (yrs) (range; SD)	74 (43 to 88; 8)	71 (41 to 83; 7)
Gender (female:male)	27:23	29:21
Mean body mass index, kg/m ² (SD)	32.6 (7.3)	34.1 (5.3)
Smokers	16	19
Alcohol > weekly recommended units	11	5
ASA grade, patient (n)	1, 0	1, 0
	2, 19	2, 22
	3, 34	3, 34
	4, 7	4, 4
Diabetes mellitus	7	5
Primary diagnosis		
Rheumatoid arthritis	7	3
Osteoarthritis	43	47
Type of total hip arthroplasty		
Primary	32	29
Revision	18	21
Type of fixation		
Cemented	29	22
Cementless	21	28
Source of referral		
In-house	8	4
Referral from elsewhere	42	46
Sinus		
Yes	2	9
No	48	41
Vascular disease		
Yes	11	7
No	39	43
Pre-operative Harris Hip Scores ²⁰ (range)	44 (30 to 68)	40 (27 to 70)

ASA, American Society of Anesthesiologists

inflammatory markers show no evidence of infection, antibiotic treatment is stopped for two weeks when the patient is reviewed again. Once satisfactory, the second stage can proceed. This involves removal of the spacer and cement mantle, piecemeal if necessary to preserve bone stock. More samples are obtained at this point and appropriate cemented components are re-implanted. Allograft may be used in patients with severe bone loss.¹⁹ At this stage, once more, all samples in the culture-negative group were negative.

It is important to note that all samples in the culture-negative cohort were negative before the first stage (during aspiration), during first-stage (implant removal) and second-stage (re-implantation).

All patients were then reviewed at six weeks, six months, one year and yearly thereafter looking carefully for symptoms and signs of infection and recording inflammatory markers (ESR, CRP and WCC).

Functional outcomes were assessed using the Harris Hip Scores (HHS).²⁰ Plain radiographs, including anteroposterior (AP) and lateral views, were obtained at each time to identify radiographic signs of infection such as progressive lucencies using radiological criteria outlined by Johnston et

al.²¹ The eradication of infection is defined as the absence of clinical, serological, and radiographic signs at any subsequent time. The Musculoskeletal Infection Society (MSIS) criteria were used at the final review to confirm the control of infection.^{16,22} Failure was defined as any major operation performed in any patient for the control of infection, including further two-stage revision, excision arthroplasty, arthrodesis, amputation or the need for long-term antibiotic suppression.

The groups were compared using the following variables: age, gender, BMI, smoking, alcohol, American Society of Anesthesiology (ASA) grade,²³ diabetes, primary diagnosis (rheumatoid or osteoarthritis), type of THA (primary or revision), type of fixation (cemented or cementless), source of referral (from our institution or from elsewhere), the presence of a sinus and vascular disease.

Statistical analysis. A chi-squared test was employed to identify differences between categorical variables and outcomes. The Mann-Whitney U test and two-sample student *t*-tests were used to compare continuous variables and outcomes between the two groups using SPSS version 20 (IBM, Armonk, New York). A multiple logistic regression analysis was performed to identify the independent influence of

Table V. Isolated micro-organisms for the culture-positive group

Microorganisms	Patients (n)
Gram-positive	30
Gram-negative	13
Anaerobes	9
Mycobacterium	0
Polymicrobial	8

Table VI. Outcomes of culture-negative and culture-positive groups

	Culture -ve group (n = 50)	Culture +ve group (n = 50)	p-value
Mean post-operative HHS	83 (SD 9)	85 (SD 8)	0.34*
Further revision	3	4	0.14 [†]
Repeat first stage procedures	5	2	0.09 [†]
Dislocation	4	3	0.062 [†]
Fracture	1	1	0.24 [†]
Recurrent infection	3	3	0.19 [†]

*p-value calculated using Mann-Whitney U test

[†]p-value calculated using chi-squared test

HHS, Harris Hip Score

Table VII. Multivariate analysis on significant risk factors from univariate analysis

Factor	Univariate (p-value)	Multivariate results (odds ratio)	Multivariate results (p-value)*
Age (yrs)	0.003	2.4	0.32
Smoking	0.037	2.1	0.56
Pre-operative antibiotics	0.002	4.1	0.003
Referral from elsewhere	0.0016	3.1	0.001

*p-values calculated using multivariate logistic regression analysis

each variable in Table IV on developing culture-negative samples in PJI in a forward stepwise model. A p-value of < 0.05 was considered significant.

Departmental approval was obtained to conduct this study.

Results

There were 50 consecutive patients in each group. The mean age was 74 years (43 to 88) in the culture-negative group and 71 years (41 to 83) in the culture-positive group. Both groups had more women than men. There were no significant demographic differences between the groups (Table IV). Most of the micro-organisms isolated in the culture-positive group were gram-positive bacteria (Table V).

There were no differences in functional outcomes between the groups. The mean Harris hip scores (HHS) were 83 (SD 9) and 85 for the culture-negative and culture-positive group respectively; this difference was not statistically significant (p = 0.34). Three patients in the culture-negative group and four in the culture-positive group required further revision surgery but again this difference was not statistically significant (p = 0.14). Five patients in the culture-negative group had several first-stage procedures compared with two in the culture-positive group, but this was not significant (p = 0.09). There were no other differences in the complications (Table VI). The rate of re-

infection at five years was 6% for both groups. *Staphylococcus epidermidis* was cultured at a further staged revision in the three patients with a recurrent infection. In the culture-positive group, two patients had polymicrobial cultures in their staged revision and one had *staphylococcus epidermidis*. The fourth patient was revised due to multiple dislocations and instability and had a diagnosis of infection in the last operation and remains as such.

Univariate analysis identified the following risk factors for culture-negative samples: age, referral from elsewhere, smoking and pre-operative antibiotics these were entered into multivariate logistic regression model to reveal preoperative antibiotics and referral from elsewhere as the most significant risk factors for culture-negative group (Table VII).

Five patients in the culture-negative group were lost to follow-up after the five-year mark, three in the culture-positive group were lost after the fourth year but they have not had further surgery. It is possible that these patients may have passed away and therefore lost to follow-up.

Discussion

We found no significant differences in outcomes between culture-negative and culture-positive patients following two-stage revision THA at medium term follow-up. The rate of re-infection for both culture-negative and culture-positive groups was 6% five years post-operatively, in line

Table VIII. Rate of infection-free survival for studies dealing with culture-negative infected total hip arthroplasties undergoing two-stage revision

Study	Rate of control of infection (%)	Mean follow-up (yrs)
Berbari et al ⁸	94	5
Malekzadeh et al ²⁶	78	4.6
Bejon et al ⁶	83	5.7
Huang et al ²⁴	70	3.9
Choi et al ²⁵	85	4
Our study	94	5

with other published studies dealing with culture-negative PJIs.^{8,24} There were no significant differences in the outcomes between both groups, this is in line with other published studies.²⁴ Choi et al,²⁵ on the other hand, found that culture-negative patients (n = 40) have a better rate of infection control (p = 0.006) than culture-positive patients (n = 132) with mean follow up of four years, but this cohort included total knee replacements as well as THAs; our study is concerned with THA only. In our study, the selection of patients was also different as straight-forward cases were treated with a single-stage revision, and the more complex cases with more virulent organisms underwent two-stage revision. Culture-negative patients were treated identically to complex, culture-positive patients with aggressive debridement and antibiotics recommended by multidisciplinary collaboration.¹⁸ This should be taken into account when comparing the rate of control of infection in this study with others (Table VIII).

These findings suggest that more extensive, invasive and expensive investigations such as arthroscopic sampling following aspiration and biopsy,²⁷ are unnecessary, as these patients should be treated as having a complex culture-positive PJI. They should not be treated with a single-stage revision.¹¹

There are many risk factors contributing to infection in general and these are shared for the culture-negative and culture-positive groups. These include immunocompromised patients and those with multiple comorbidities.²⁸⁻³⁰ Many authors have described the risk factors, including age, gender, comorbidities and BMI, associated with culture-negative PJI in general, usually with a mixture of arthroplasties of the hip, knee and shoulder.^{7,31} In our study, gender and BMI were not significant factors but age was identified as a risk factor for culture-negative PJI. Smoking is a known risk factor for culture-negative PJI in several studies^{7,31} and this was replicated in our study. Many authors have reported that taking antibiotics within three months of obtaining samples was a significant risk factor for culture-negative PJI,^{7,25,26,28-30} this was also replicated in our study, although we only included THAs.

Although the risk factors are well described in the literature, we identified a factor not previously considered: referral from elsewhere. This may be related to the pre-operative use of antibiotics, as most of these patients were referred several months after the start of infection. Patients from our

institution all had positive cultures, probably as strict protocols are in place for the management of a PJI. It is difficult to control the use of antibiotics prior to specialist intervention. However, educating healthcare providers may reduce this; specifically, general practitioners and emergency medicine doctors.

In spite of extended cultures and PCR, no organism was identified at any point on the culture-negative patients, in contrast to Bereza et al³² who were able to identify organisms at a later stage, or following further investigations such as sonication and PCR testing.

Limitations of this study include the small sample size for both groups and the lack of randomisation. The consecutive nature of the cohort of patients helps to avoid selection bias. Longer follow up would improve the identification of rates of recurrent infection. However, most studies in the literature have a similar follow-up.

In conclusion, we found that in spite of negative cultures in patients with PJI after THA, effective treatment is achievable by treating these patients as if they were complex culture-positive patients with a two-stage revision and strict protocols. The outcomes with such management are similar to the management of culture-positive patients.



Take home message:

- Aseptic joint infection is a complex problem and should be considered as such.
- Culture-negative infections can be eradicated with a two-stage revision approach, following strict protocols.
- Outcomes of culture-negative PJIs are similar to complex patients with positive cultures.
- Reducing culture-negative infections can be achieved with education regarding antibiotic usage in the community

Author contributions:

M. S. Ibrahim: Writing and editing the paper, Analysed data.

H. Twaij: Writing and editing the paper.

F. S. Haddad: Senior author, Designed the study, Writing and editing the paper.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

This article was primary edited by J. Scott.

This paper is based on a study which was presented at the 33rd annual Winter 2016 Current Concepts in Joint Replacement meeting held in Orlando, Florida, 14th to 17th December.

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