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■ GENERAL ORTHOPAEDICS

Should all patients with a culture-negative periprosthetic joint infection be treated with antibiotics?

A MULTICENTRE OBSERVATIONAL STUDY

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Aims

The aim of this study was to analyze the prevalence of culture-negative periprosthetic joint infections (PJIs) when adequate methods of culture are used, and to evaluate the outcome in patients who were treated with antibiotics for a culture-negative PJI compared with those in whom antibiotics were withheld.

Methods

A multicentre observational study was undertaken: 1,553 acute and 1,556 chronic PJIs, diagnosed between 2013 and 2018, were retrospectively analyzed. Culture-negative PJIs were diagnosed according to the Musculoskeletal Infection Society (MSIS), International Consensus Meeting (ICM), and European Bone and Joint Society (EBJIS) definitions. The primary outcome was recurrent infection, and the secondary outcome was removal of the prosthetic components for any indication, both during a follow-up period of two years.

Results

None of the acute PJIs and 70 of the chronic PJIs (4.7%) were culture-negative; a total of 36 culture-negative PJIs (51%) were treated with antibiotics, particularly those with histological signs of infection. After two years of follow-up, no recurrent infections occurred in patients in whom antibiotics were withheld. The requirement for removal of the components for any indication during follow-up was not significantly different in those who received antibiotics compared with those in whom antibiotics were withheld (7.1% vs 2.9%; $p = 0.431$).

Conclusion

When adequate methods of culture are used, the incidence of culture-negative PJIs is low. In patients with culture-negative PJI, antibiotic treatment can probably be withheld if there are no histological signs of infection. In all other patients, diagnostic efforts should be made to identify the causative microorganism by means of serology or molecular techniques.

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Introduction

The prevalence of culture-negative periprosthetic joint infections (PJIs) reported in the literature is high; varying between 5% and 42%, with an average of 11%.¹ Due to the recent introduction of more sensitive diagnostic criteria for PJI² than those proposed by the Musculoskeletal Infection Society (MSIS)³ and International Consensus Meeting (ICM),⁴ the number of patients diagnosed as having a culture-negative PJI is likely to increase even further as the threshold for the diagnosis of infection decreases. According to the

definition of PJI by the European Bone and Joint Society (EBJIS), infection is confirmed if only one criterion for infection is positive.² Although low-grade PJIs will be less likely to be missed according to this definition, there will be a risk of overdiagnosis and overtreatment, in particular when cultures remain negative, although the patient meets the criteria for PJI.

Although some authors have reported that patients who underwent revision arthroplasty due to a PJI based on only minor diagnostic criteria have a worse outcome compared with those who

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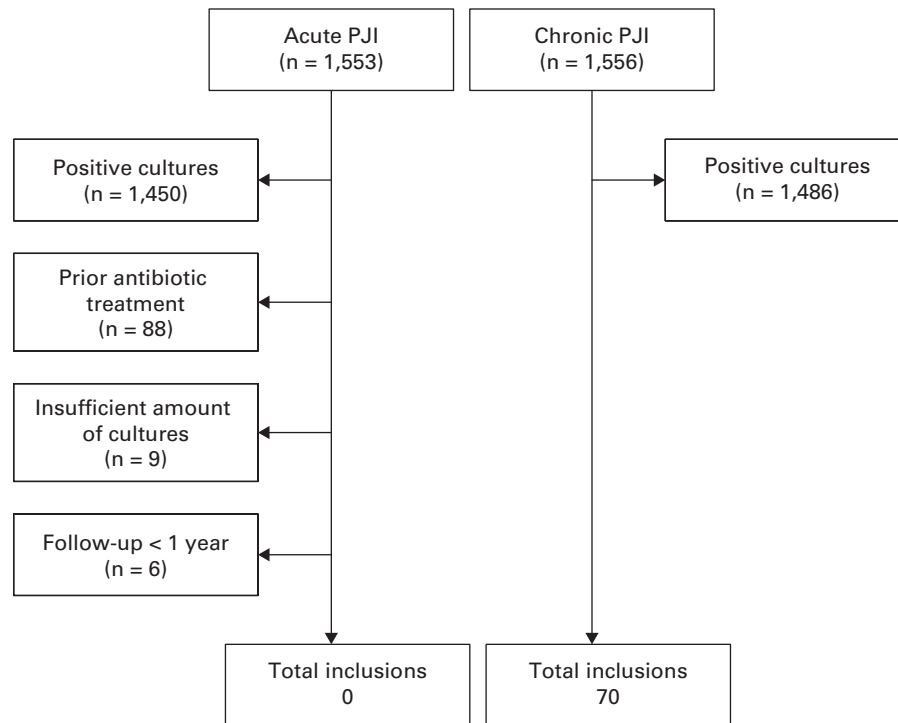


Fig. 1

Flowchart of those who were included. PJI, periprosthetic joint infection.

underwent revision for aseptic indications,⁵ none have evaluated whether antibiotic treatment improves the outcome of the first group of patients. It could be that the minor diagnostic criteria for PJI are just a surrogate marker for a vulnerable host and/or an inflammatory state as reaction to foreign material, instead of being a true sign of infection. It is also unclear whether the high rate of culture-negative PJIs which has been reported can be mainly attributed to previous antibiotic treatment and/or due to the use of inadequate methods of culture. We hypothesized that the prevalence of culture-negative PJI would drastically decrease when adequate methods of culture are used, and that the remaining patients with negative cultures who still fulfill the definition of PJI do not require antibiotic treatment if atypical microorganisms are ruled out.

The aims of this study were two-fold: to determine the prevalence of culture-negative PJIs according to the MSIS, ICM, and EBJIS definitions in an established cohort of patients with PJI in whom adequate methods of culture were used; and to determine whether culture-negative PJIs have a better clinical outcome when treated with antibiotics compared with those in whom antibiotics are withheld.

Methods

All patients with an arthroplasty of the hip or knee who underwent surgery for infection (debridement, antibiotics and implant retention (DAIR) and one- or two-stage exchange) between January 2013 and January 2018 were retrospectively evaluated. Patients in whom at least four intraoperative periprosthetic tissue samples, or at least three intraoperative periprosthetic tissue samples plus sonication fluid, were obtained

for culture were included. The periods of incubation for culture which were required were: \geq five days for acute infections;⁶ \geq nine days for chronic infections when inoculating synovial fluid and/or tissue cultures and/or sonication fluid in blood culture bottles;^{7,8} or \geq 14 days when not using any of these techniques.⁹ The following exclusion criteria were applied: patients with \geq one positive culture; those who received antibiotics prior to revision surgery (unless discontinued at least two weeks before surgery);¹⁰ and those with follow-up of less than one year for acute infections and less than two years for chronic infections.

The administration of antibiotic prophylaxis prior to surgery was not considered an exclusion criterion.¹¹ The primary endpoint of the study was recurrent infection after a two-two-year follow-up period. The secondary endpoint was removal of the prosthetic components during this time for any indication. Ethical approval and informed consent were obtained according to the requirements of the participating centres.

For patients with an acute infection (< six weeks after the index surgery), the diagnosis of culture-negative PJI was based on the following criteria:

According to the ICM (2018) definition \geq six points: two points for an elevated serum CRP (> 100 mg/l), three points for a synovial leucocyte count of $> 10,000$ cells/ μ l or a positive α defensin in the synovial fluid or ++ leucocyte esterase in the synovial fluid, two points for $> 90\%$ polymorphonuclear leucocytes (PMNs) in the synovial fluid, and three points for positive histology (≥ 5 neutrophil per high power field (HPF)).⁴

According to the MSIS (2013) definition, three of the following: an elevated ESR (> 30 mm/h) and CRP (> 10 mg/l),

positive histology (≥ 5 neutrophils per HPF), a synovial leucocyte count of $> 3,000$ cells/ μ l or ++ change on a leucocyte esterase strip, and $> 80\%$ PMNs in the synovial fluid.³

According to the ICM (2018) definition \geq six points: two points for an elevated serum CRP (> 10 mg/l) or serum D-Dimer > 860 μ g/l, one point for an elevated ESR (> 30 mm/h), three points for positive histology (≥ 5 neutrophils per HPF), three points for a synovial leucocyte count of $> 3,000$ cells/ μ l, a positive α defensin, or ++ leucocyte esterase in the synovial fluid, and two points for $> 70\%$ PMNs in the synovial fluid.⁴

According to the EBJIS (2020) definition, any of the following: positive histology (≥ 5 neutrophil per HPF) or a synovial leucocyte count of $> 3,000$ cells/ μ l or $> 80\%$ PMNs.²

For patients with a chronic infection (presenting > 6 weeks after surgery) the diagnosis of culture-negative PJI was based on the following criteria:

According to the MSIS (2013) definition, three of the following: elevated ESR (> 30 mm/h > 10 mg/l), positive histology (≥ 5 neutrophils per HPF), $> 3,000$ cells/ μ l or ++ change on leucocyte esterase strip, and $> 80\%$ PMNs in synovial fluid.

According to the ICM (2018) definition \geq six points: two points for an elevated serum CRP (> 10 mg/l) or serum D-Dimer > 860 μ g/l, one point for an elevated ESR (> 30 mm/h), three points for ≥ 5 neutrophils per HPF, three points for $> 3,000$ cells/ μ l, positive α defensin, or ++ leucocyte esterase in synovial fluid, and two points for $> 70\%$ PMNs in synovial fluid.

According to EBJIS (2020) definition, any of the following: positive histology (≥ 5 neutrophil per $> 3,000$ cells/ μ l), or $> 80\%$ PMNs.

All of the above needed to be accompanied by negative cultures. The cut-off in colony-forming units to determine that a culture was negative depended on local microbiological protocols. Patients with a sinus tract communicating with the joint were considered to be infected according to all definitions.

Statistical analysis. A chi-squared test was used to analyze the difference between groups for categorical variables. A Kaplan-Meier survival curve with a Cox regression analysis was used to evaluate failure due to recurrent infection and removal of the prosthetic components for any indication at any time. Logistic regression analysis was performed to identify independent risk factors for failure. Variables with a difference between groups, defined as a p-value < 0.2 in the univariate analysis, were included in the multivariate analysis. Significance was defined as a two-tailed p-value < 0.05 . Analyses were performed using IBM SPSS Statistics (v. 24.0; USA).

Results

A total of 1,553 acute and 1,556 chronic PJIs from 17 centres were evaluated (Figure 1). According to the inclusion and exclusion criteria, none of the acute PJIs met the definitions for culture-negative infection. From the chronic PJIs, 70 patients from nine centres met the criteria for culture-negative infection (4.7%), and were included in the study. A total of 69 met the criteria of culture-negative PJI according to the EBJIS definition (99%), 28 according to the MSIS definition (40%), and 18 according to the ICM definition (26%) (Figure 2).

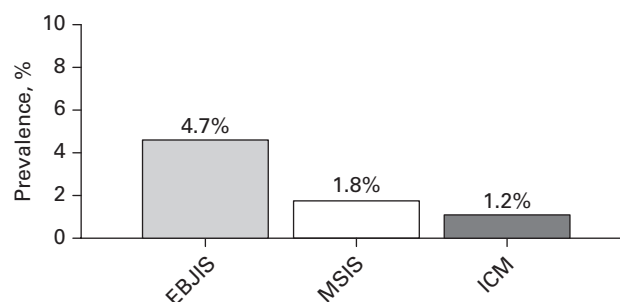


Fig. 2

Prevalence of culture-negative periprosthetic joint infections (PJIs) according to the different diagnostic criteria. EBJIS, European Bone and Joint Infection Society; ICM, International Consensus Meeting; MSIS, Musculoskeletal Infection Society.

Most patients with a PJI were treated with revision surgery: one-stage revision in 27 patients (38%), two-stage revision in 34 (49%), and debridement in nine (13%). All those who underwent debridement were treated ≥ 6 weeks but < 3 months after the surgery.

Additional molecular testing, using either 16 S RNA sequencing or species-targeted polymerase chain reaction, was undertaken in 14 patients (20%). Three of these patients (21%) tested positive, with *Cutibacterium acnes*, *Streptococcus* species, and *Streptococcus dysgalactiae*, respectively. All three had positive histology for infection and were successfully treated with antibiotics. In 11 patients (16%), synovial fluid was examined for crystals; one (9.1%) was positive. Metallosis was observed in histological sections from tissue biopsies in 18 patients (26%).

A total of 36 patients (51%) with a culture-negative PJI were treated with antibiotics for a minimum of six weeks and a maximum of six months. One patient received lifelong antibiotic suppressive therapy. A total of 11 patients (31%) were treated with a rifampin-based regimen, mostly combined with a fluoroquinolone as co-antibiotic. Most of those who were treated with monotherapy received oral clindamycin or linezolid.

The choice and duration of antibiotic treatment was at the discretion of the treating physician and according to local protocols.

Table I shows the characteristics of the patients who were treated with antibiotics compared with those in whom antibiotics were withheld. Those with positive histology for infection and those with culture-negative PJI according to the ICM criteria were more frequently treated with antibiotics. Other parameters associated with antibiotic treatment included an increased synovial leucocyte count, a serum CRP of > 10 mg/l, and those with arthroplasty of the knee. Most of those treated with antibiotics underwent a DAIR or two-stage revision surgery. A one-stage revision was more often seen in the group in whom antibiotic treatment was withheld.

We analyzed the failure rate after revision surgery for a culture-negative PJI during a follow-up of two years, including recurrent infection and removal of the prosthetic components for any indication. There were no deaths during

Table I. Table I. Patient characteristics for culture-negative periprosthetic joint infections according to antibiotic treatment.

Variable	No antibiotic treatment	Antibiotic treatment	p-value*
Patients, n	34	36	
Baseline characteristics, % (n)			
Male sex	50 (17)	50 (18)	1.003
Age > 80 yrs	9 (3)	6 (2)	0.601
BMI > 30 kg/m ²	50 (17)	57 (20)	0.551
Medical history, % (n)			
Diabetes	32 (6/19)	20 (7/35)	0.341
Renal failure	5 (1/19)	6 (2/35)	0.951
COPD	0 (0/19)	6 (2/35)	0.292
Liver cirrhosis	5 (1/19)	0 (0/35)	0.170
Rheumatoid arthritis	9 (3/34)	11 (4/36)	0.751
Implant characteristics, % (n)			
Hip	38 (13/34)	14 (5/36)	0.021
Knee	62 (21/34)	86 (31/36)	0.021
Primary prosthesis	74 (25/34)	75 (27/36)	0.890
Tumour prosthesis	6 (2/34)	0 (0/36)	0.142
Cemented	74 (14/19)	74 (25/34)	0.990
Clinical presentation, % (n)			
Joint effusion	24 (8/33)	36 (13/36)	0.282
Prosthetic loosening	47 (16/34)	44 (16/36)	0.831
Sinus tract	32 (11/34)	47 (17/36)	0.21
Inflammatory markers, % (n)			
Serum CRP > 10 mg/l	45 (15/33)	78 (25/32)	0.007
Serum ESR > 30 mm/h	50 (15/30)	68 (13/19)	0.201
Synovial leucocytes > 3,000 cells/ μ l	29 (2/7)	92 (11/12)	0.004
Synovial PMN > 80%	38 (3/8)	43 (6/14)	0.701
Histology, % (n)			
Infection	23 (5/22)	91 (20/22)	< 0.001
Metallosis	55 (17/31)	4 (1/27)	< 0.001
Surgery, % (n)			
DAIR	2.9 (1/34)	22.2 (8/34)	
One-stage revision	61.8 (21/34)	16.7 (6/34)	
Two-stage revision	35.3 (12/34)	61.1 (22/34)	
Culture-negative PJI criteria, % (n)			
EBJIS definition	97 (33/34)	100 (36/36)	0.302
MSIS definition	32 (11/34)	47 (17/36)	0.201
ICM definition	15 (5/34)	94 (34/36)	0.041

*Chi-squared test.

COPD, chronic obstructive pulmonary disease; DAIR, debridement, antibiotics, and implant retention; EBJIS, European Bone and Joint Infection Society; ICM, International Consensus Meeting; MSIS, Musculoskeletal Infection Society; PJI, periprosthetic joint infection; PMN, polymorphonuclear leucocytes.

this time. Three patients (4.3%) had a recurrent infection. All these patients were treated with antibiotics during the initial episode of culture-negative PJI. Two were treated with oral clindamycin for three months. Treatment in the other patient failed while receiving intravenous cefepime and daptomycin. No infections occurred during this period of time in patients with a culture-negative infection in whom antibiotic treatment was withheld (Figure 3a). Table II shows the rate of

Table II. Table II. Recurrent infection during follow-up according to the different definitions of periprosthetic joint infection.

Definition	Overall, % (n)	Antibiotic treatment, % (n)	No antibiotic treatment, % (n)
EBJIS (n = 69)	4.3 (3/69)	8.3 (3/36)	0 (0/33)
MSIS (n = 28)	3.6 (1/28)	5.9 (1/17)	0 (0/11)
ICM (n = 18)	11.1 (2/18)	15.4 (2/13)	0 (0/5)

EBJIS, European Bone and Joint Infection Society; ICM, International Consensus Meeting; MSIS, Musculoskeletal Infection Society.

recurrent infection during this time according to the different definitions of PJI which were used. All three patients with a recurrent infection had a culture-negative PJI according to EBJIS definition, two according to the ICM definition, and one according to the MSIS definition. In those in whom antibiotics were withheld, five patients had a recurrent infection according to the ICM definition, 11 according to the MSIS definition, and 33 according to the EBJIS definition. Treatment was successful in all these patients during the two-year follow-up period.

Removal of the components for any indication during follow-up was seen in three patients, all due to aseptic loosening. The requirement for this was the same in patients treated with antibiotics compared with those in whom antibiotics were withheld (7.1% vs 2.9%; $p = 0.431$) (Figure 3b).

Discussion

In this multicentre retrospective observational study, we found a low incidence of culture-negative PJIs when applying strict inclusion criteria for culturing, and when excluding patients who received antibiotic treatment prior to surgery. Using these criteria, no culture-negative PJIs were identified in acute infections, and only 4.7% of chronic infections were culture-negative. The highest yield of culture-negative patients was identified when using the recently introduced EBJIS definition criteria.² We found that those patients who were considered the most likely to be infected, such as those with positive histology for infection, were treated with antibiotics while less obviously infected patients were less likely to be treated with antibiotics. There were no recurrent infections during a two-year follow-up period in the patients from whom antibiotic treatment for culture-negative PJI was withheld, nor did they have a higher rate of removal of the prosthetic components.

The low prevalence of culture-negative PJI we found in our strictly defined population confirmed the hypothesis that insufficient methods of culture and previous antibiotic treatment mostly contribute to culture negativity. This was particularly evident for acute infections, with no acute culture-negative infections in the study group. This can be explained by the fact that planktonic bacteria are easier to detect compared with stationary bacteria embedded in chronic biofilms.⁶ By using more sensitive criteria for the diagnosis of PJI the prevalence of culture-negative PJIs increased, but still remained below 5%. The prevalence of culture-negative infections may be underestimated in our study, since the complete diagnostic work-up, including all minor criteria of infection, was not performed in patients with a very low chance of infection undergoing

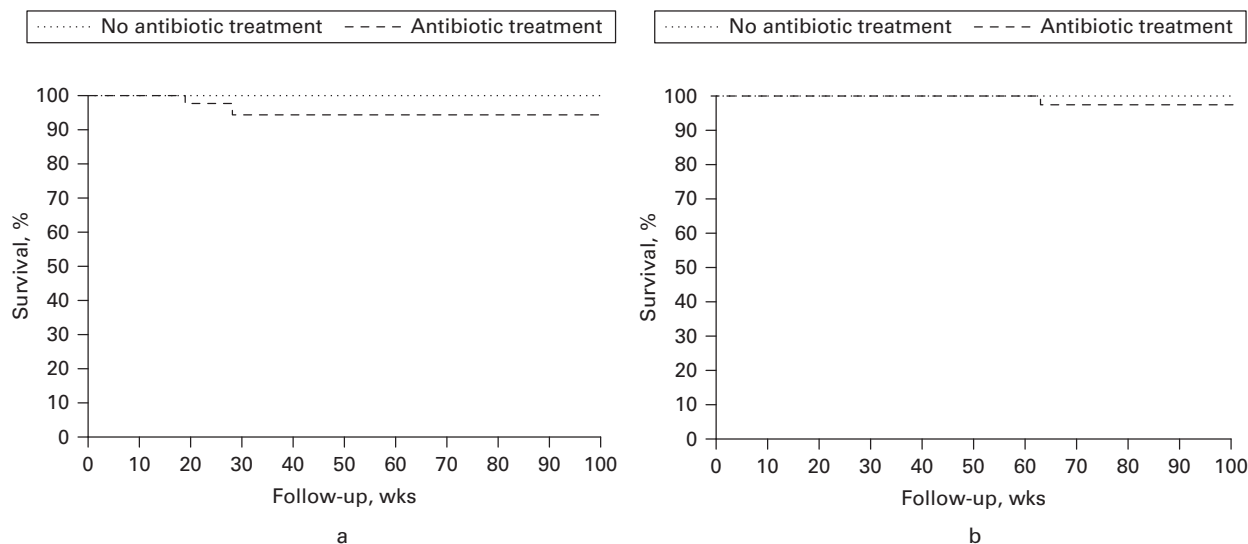


Fig. 3

Survival of culture-negative periprosthetic joint infections (PJIs) according to antibiotic treatment; the outcome of culture-negative PJIs according to antibiotic treatment ($n = 36$) versus no antibiotic treatment ($n = 34$). Classified into a) recurrent infection and b) removal of prosthetic components during a follow-up of two years. CI, confidence interval; HR, hazard ratio.

revision surgery, such as those with obviously malaligned components.¹² In addition, D-dimer measurement, as part of the ICM criteria, was not performed since its introduction for the diagnosis of PJI appeared after the period of study. As a consequence, culture-negative PJIs are potentially underdiagnosed when using the MSIS and ICM criteria in our analysis, since not all tests that make up the criteria were performed in our patients. The exact prevalence of culture-negative PJIs should be identified in prospective trials using stringent systematic diagnostic protocols.

To our knowledge, we are the first, however, to report the effect of antibiotic treatment compared with no antibiotic treatment in patients with a culture-negative PJI. In a systematic review and meta-analysis undertaken by Reisener and Perka,¹³ treatment was successful in between 85% and 95% of culture-negative PJIs. Most were treated with antibiotics. They concluded that the outcome of culture-negative PJIs is similar, if not better, when compared with the treatment of culture-positive PJIs. This may be explained either by the low inoculum of bacteria in culture-negative infections, making the eradication of infection easier compared with culture-positive infections, or by the hypothesis that the culture-negative group included patients who were wrongly classified as infected (e.g. due to the presence of (false) positive criteria for infection in those with gout or other inflammatory conditions). The success rate in patients treated with antibiotics in our study was similar to that reported by Reisener and Perka:¹³ $13 \pm 95\%$ when recurrent infection during follow-up was considered as failure. Since the antibiotic-treated group in our study included patients with a higher likelihood of infection (for example, those with histological signs of infection) we are unable to advise against antibiotic treatment in this particular group of patients. Our analysis showed the importance of additional serology and/

or molecular testing in these patients in an attempt to find the causative organism. In our study, only 20% of patients received additional molecular testing, either via sequencing of the 16 S ribosomal region or species targeted. In those cases in whom additional testing was performed, a positive signal was only found in patients with positive histology for infection and, in addition, treatment was successful in all the patients in whom molecular testing identified the organism, and thus, treatment could be tailored. In a recently published retrospective study performed by Wang et al,¹⁴ culture-negative PJIs treated with empirical antibiotic treatment were compared with those who received targeted antibiotic treatment based on next generation sequencing results. Unfortunately, the sample size was too small to draw definitive conclusions, but two of 13 patients who were treated with empirical treatment required further debridement, while none of 14 in the targeted group required further surgery for infection. Larger analyses are required to establish whether molecular sequencing really improves the outcome in these patients.

Our most interesting finding was that treatment was successful in all the patients in whom antibiotics were withheld during the two-year follow-up period. This indicates that when less stringent criteria are used for the diagnosis of infection, thus when the threshold for the diagnosis of infection decreases, more patients will be over-diagnosed. Although we cannot exclude the possibility that treatment will fail in these patients after two years, it is known that most PJIs present during the first two years after surgery.¹⁵ Thus, withholding antibiotics in culture-negative PJIs, in particular in patients without histological signs of infection or those who do not fulfill the ICM criteria, is probably justified. However, the number of patients, who were analyzed was limited in this study and larger prospective trials are needed to confirm the findings.

In conclusion, due to the lack of complete diagnostic investigations, the exact incidence of culture-negative PIJs is not known, but appears low when adequate methods of culture are used. In patients with culture-negative PJI, antibiotics can probably be withheld if there are no histological signs of infection. In all other patients, diagnostic efforts should be made to identify the causative organism using serology or molecular techniques. Larger prospective trials are needed to identify exactly which patients benefit from antibiotic treatment, and which do not require antibiotics.



Take home message

- Adequate culture methods reduce the prevalence of culture-negative periprosthetic joint infections (PJIs).

- If a culture-negative PJI is diagnosed based on positive infection histology, maximal attempts should be made to find the causative microorganism by means of molecular techniques and/or serology.

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