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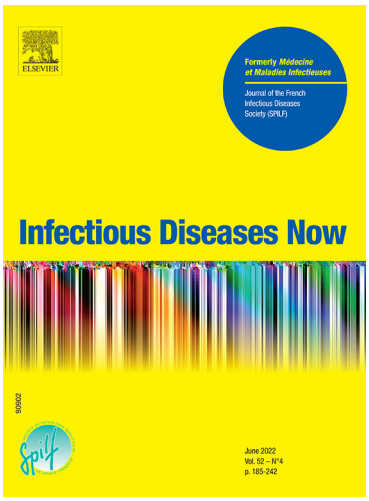

Original article

Can we rely on histopathological results for the diagnostic of prosthetic joint infection?

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Can we rely on histopathological results for the diagnostic of prosthetic joint infection?

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Highlights

- Concordance of histology with sinus tract communication and/or at least two positive cultures was 74.1%

- Histopathological examination remains a criterion of prosthetic joint infection (PHI) for the different academic societies

- The sensitivity and specificity of histopathology were 61% and 92% respectively
  - Histopathological result is relevant when it shows signs of infections (acute inflammation)
- 'Histopathology-culture' sample pairs from the same intraoperative location should be performed
  - During a revision surgery for suspected PJI, at least one sample of periprosthetic needs to be sent to a specialized pathologist (periprosthetic interface membrane and/or neosynovium)
- The highest correlation is observed for very early infection and for virulent microorganisms, such as Staphylococcus aureus, Streptococci or Enterobacterales.
  - Histopathological results need to be interpreted with caution in low-grade infection.

Abstract

Background

Histopathology is one of the diagnostic criteria for prosthetic joint infection (PJI) proposed by all academic societies. The aim of this study was to compare histopathological and microbiological results from samples taken intraoperatively at the same site in patients with suspected or proven PJI.

Patients and methods

We conducted a monocenter retrospective study including all patients having undergone surgery from 2007 to 2015 with suspected or proven PJI. During surgery, both histopathological and microbiological samples were taken. Patients with a history of antimicrobial treatment 2 weeks prior to surgery were excluded. We considered as major criteria and gold standard for PJI diagnosis the presence of a sinus tract communication and/or the same microorganism in at least two cultures.

Results

Finally, 181 patients who underwent 309 surgeries were included. The median number of samples per surgery was 4 (interquartile range (IQR) = 3-5) for histopathology and 5 (IQR=4-6) for microbiology. Major criteria were observed in 177 patients (57.3%), while positive histology in at least one intraoperative sample was present in 119 (38.5%). The concordance was 74%. The sensitivity and specificity of histopathology were 61% and 92% respectively. Available "histopathology-culture" sample pairs numbered 1247. Among them, positive histopathology was found in 292 samples (23%) and culture in 563 (45%). Concordance was 64%. The highest correlation was observed for very early infection (< 1 month) (OR: 9.1, 95% CI: 3.6-23) and for virulent microorganisms, such as *Staphylococcus aureus* (OR: 7.8, 95% CI: 5.2-11.8), *Streptococci* (OR:7.8; 95% CI: 4-15.2) or Enterobacterales (OR: 7.4; 95% CI: 4.2-13.1).

Conclusion

Histopathologic examination is a valuable criterion for PJI diagnosis, but it may lack sensitivity for chronic infections or due to low-virulence pathogens.

Keywords: Anatomy and histology; Prosthesis and Implant Infections; Joint Prosthesis; Device Removal

Introduction

Prosthetic joint infection (PJI) is a rare but severe complication after total joint arthroplasty. Even though incidence is low, approximately 1.7/100 person-years for hip and knee arthroplasties in France, the number of prosthetic joint implementation procedures has increased over time [1]. Therefore, the total number of diagnosed and managed PJI is expected to rise accordingly. The proper diagnosis of PJI is consequently crucial for adequate treatment. Several academic societies have proposed diagnostic criteria for PJI [2–7] (see Appendix). Histopathological analysis is one of these criteria. Most of the time classified as a minor criterion, it is nonetheless considered by many authors to be a helpful parameter in doubtful situations.

We attempted to determine the value of histopathology in a large single-center study including consecutive patients with proven or suspected PJIs.

Patients and Methods

We conducted a retrospective study in a general community hospital in France, where a dedicated team for the management of complex bone and joint infections was created in 2007. The team includes two surgeons specialized in prosthetic joint revision, two clinical microbiologists, two infectious disease specialists, two pharmacists and one medical practitioner in charge of day-to-day management of patients in the postoperative period.

In our center, the perioperative surgical protocol for suspected or definite PJI is to take three to six periprosthetic samples and to cut all of them into two parts, one for microbiological

procedures and one for histopathological analysis. The different types of samples include neosynovium, periprosthetic membrane, bone tissue, collections, hematoma, or synovial fluid. Because of the proximity of the microbiological laboratory to the operating room in our hospital, samples are processed within one hour of their completion.

In the laboratory, bone and soft tissues were disrupted (Retsch MM400™, Fisher Scientific, Illkirch, France). All samples were plated into two Columbia 5% sheep blood agar plates (aerobic and anaerobic atmosphere), one chocolate Polyvitex agar plate (CO2 atmosphere) (Biomerieux, Marcy L'Etoile, France), and thioglycolate broth (Oxoid, Dardilly, France). All samples were incubated at 35±2°C for 14 days. Cultures were observed for 14 days, and thioglycolate broth was subcultured into the same solid media if all cultures were negative after eight days. If cultures were positive, microorganisms were identified by a biochemical method on a Vitek 2 Compact™ (BioMerieux, Marcy l'Etoile, France). Antibiotic susceptibility was also determined on a Vitek 2 Compact™ by broth microdilution and interpreted according to the CA-SFM/EUCAST recommendations [8].

Histological analysis was performed by a pathologist specialized in musculoskeletal diseases. Samples were sent following fixation in formalin. Paraffin block sections were obtained and stained with hematoxylin and eosin. The slides were postoperatively studied under normal and polarized light microscopy.

All patients (≥ 18 years) having undergone surgery for suspected or definite PJI from July 2007 to April 2015 were eligible for inclusion. We included all surgical procedures for which at least one pair of histopathology and culture results was available from the same sample. The exclusion criterion was a history of antimicrobial therapy two weeks prior to surgery.

According to the rules and regulations of clinical research for descriptive retrospective studies in France, approval of an ethics committee was not necessary, and consent was indirectly

obtained by non-opposition to the use of the data for research purposes from all patients/ parents after information was given [9].

We used the 2011 Musculoskeletal Infection Society (MSIS) definition of PJI diagnosis [5] (see Appendix): at least one of the two major criteria is sufficient to the diagnosis of PJI. The major criteria are a sinus tract communicating with the articulation and identification of the same microorganism in at least two cultures (or isolation of a single virulent organism). Diagnosis is also in favor of infection when four of the following six minor criteria exist: elevated serum erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) concentration, preoperative puncture of synovial fluid with elevated white blood cell count, elevated synovial percentage of neutrophil granulocytes (NGs), presence of purulence during the surgery, isolation of a microorganism in one culture of periprosthetic tissue or fluid and positive histology.

A new MSIS definition was published in 2018 with the same major criteria and other preoperative and intraoperative criteria rated from 1 to 3 [4] (see Appendix).

Only serum CRP, leukocyte count in the synovial fluid with percentage of NGs and histology results were available in our center, and they did not enable us to calculate a score. Presence of purulence during the surgery could not be collected.

We defined elevated serum CRP as superior to 10 mg/dL and elevated synovial leukocyte count as superior t 3000 cells/µL.

Pathogenic virulent microorganisms include *Staphylococcus aureus*, *Streptococcus sp.*, *Enterococcus sp.*, *Pseudomonas aeruginosa* and Enterobacterales. Non-pathogenic microorganisms like coagulase negative *Staphylococci* (CoNS) or *Cutibacterium acnes* are low-virulence.

According to time elapsed, PJI was defined as early if presentation occurred within three months after surgery, delayed between three and 24 months and late more than two years after surgery [6]. The retention of the prosthesis being possible within four weeks after surgery, this time limit was included [2].

Acute symptoms were defined by rapid-onset joint pain, swelling and wound purulence with or without systemic signs of infection. In contrast, chronic symptoms included grumbling discomfort, decreased range of movement and/or a sinus formation and discharge.

Each culture was classified as sterile (no microorganism isolated), contaminated (presence of a non-pathogenic microorganism not found in other samples from the same surgery) or positive (presence of one or more pathogenic microorganisms or a non-pathogenic microorganism found in two or more other samples) [10].

Positive histology was our variable of interest and was defined in accordance with Feldman *et al* [11] by the presence of more than five NGs per high power field (HPF) in five HPFs at 400x magnification. This definition was chosen by the MSIS as a criterion of PJI.

Location, histopathological and microbiological results of each intraoperative sample represented the 'histopathology-microbiology' pairs. The number of sample pairs at each surgery was notified.

Other data collected were age, sex, location of arthroplasty, bone and joint infection background, clinical presentation (acute or chronic symptoms) and presence of sinus tract communication, date of first prosthesis implantation and date of last surgery on site, preoperative explorations (CRP, synovial fluid analysis), prior antimicrobial treatment before surgery and date and type of surgical procedure for the suspected PJI (retention, one or two-stage exchange).

After a descriptive analysis of the study population, we determined the correlation between positive histology with the major criteria of PJI for all surgeries and with a positive culture at the same intraoperative site for "histopathology-microbiology" sample pairs. Sensitivity, specificity, positive and negative predictive values were calculated. Statistical analysis with the nonparametric Spearman's method resulted in a correlation coefficient between histological and microbiological results. Correlation level was determined using Stata 11®.

Results

Study population

From July 2007 to April 2015, 380 arthroplasty revisions for evident or suspected PJI were performed in 206 patients. Because of missing histopathological results, prior antimicrobial treatment or missing important data, we included 181 patients who had undergone 309 surgeries (Figure 1).

At the first surgery, the median age was 70 years (Interquartile Range (IQR) = 61-78), and 60% of the patients were male (n = 108). We noted a background of bone and joint infection in 81 patients (45%). Previous revision of the prosthesis had been carried out in 78 cases (43%); the cause was aseptic in 20 and septic in 58 (two missing data).

Characteristics of surgeries

The revision was performed on total knee arthroplasty in 154 cases (49.8%), total hip arthroplasty in 144 cases (46.6%), and on shoulder and ankle arthroplasties in six and five cases respectively (Table 1). Time between last surgery and revision for suspected PJI was early in 103 surgeries (35.1%), including 43 during the first month (14.7%), delayed in 111 (37.9%) and

late in 79 (27%). Only 21 patients (8.8%) had an acute clinical presentation before surgery, and 53 (17.1%) had a sinus tract communicating with the implant. The surgical procedure consisted of one-stage exchange in 134 (43.4%) cases and two-stage exchange in 142 (45.9%). Retention of the implant was applied in 33 (10.7%) cases.

Microbiological samples

Between one and eleven intraoperative samples were sent to the microbiology laboratory, with a median number of five samples per surgery (IQR = 4-6). During the weekly meeting of the bone and joint infection team, after multidisciplinary discussion for each surgery, contamination was considered for 84 cultures. One hundred and seventy surgeries (55%) were classified as "septic" according to the major microbiological criterion of MSIS, 142 infections were monomicrobial and 28 polymicrobial. *Staphylococcus aureus* and *Staphylococcus epidermidis* were the predominant pathogens (Table 2).

Histopathological samples

Between one and eleven intraoperative samples were sent to the pathologist, with a median number of four samples per surgery (IQR = 3-5). The pathologist found more than five NGs per HPF in five HPFs at 400x magnification in at least one intraoperative sample among 119 surgeries (38.5%).

PJI diagnosis

The MSIS criteria for PJI diagnosis in the 309 surgeries are listed in Table 3. Major criteria were encountered in 177 surgeries (57.3%) (53 with sinus tract communication and 170 with at least two microorganisms) and the four (or three without leukocyte count) minor criteria were

present in 17 surgeries (5.5%). According to the 2011 MSIS criteria, PJI was concluded in 182 cases (58.9%). Concordance between positive histology and PJI diagnosis according to 2011 MSIS criteria was 75.7%, 74.1% with major criteria and 72.5% when taking into account major microbiological criteria alone. Corresponding Odds ratios (ORs) and their 95% confidence interval (95% CI) were respectively 33 [13.8-79.1], 17.2 [8.7-34.2] and 10.8 [5.5-19.5] using logistic regression. The correlation was significant. For minor MSIS criteria, sensitivity, specificity, positive and negative predictive values were calculated considering the major criteria as the gold standard (Table 4). The sensitivity and specificity of histopathology were 61% and 92% respectively and positive and negative predictive values were 90.8% and 63.7% respectively.

When major criteria were absent (n=132), histopathology was positive in 11 cases (8.3%). Microbiology was sterile in four surgeries; CoNS was present in the seven others (four times with *C. acnes*).

Among the 127 surgeries without MSIS PJI diagnosis, six (4.7%) results of histopathology were in favor of infection and the culture was positive for two of them with *S. epidermidis.* For the other minor criteria: CRP was > 10 mg/L in 43 cases (n=80, 53.7%), synovial leukocytes were > 3000/mm^3 in 23 cases (17.4%), one single microorganism in 40 cases (31.5%).

For 220 revision surgeries (71.2%), physicians considered there was an infection and therefore a 6-to 12-week antimicrobial treatment was applied on patients. However, among these, 38 did not complete MSIS criteria for diagnosis of infection (12.3%). In three of these cases, positive histology was present, one with two concomitant positive cultures (one sample with *S. epidermidis* and one with *C. acnes*) and two with sterile cultures.

'Histopathology-microbiology' sample pairs

All in all, 1248 sample pairs from the same intraoperative sample with an available result for microbiology and histopathology were analyzed. The tissue was neosynovium and periprosthetic membrane in 55.5%, osteofibrous periprosthetic tissue in 16.2%, synovial liquid in 23.1%, tissue from the sinus tract in 3.7%, abscess in 0.9% and others in 0.6%. A positive culture was observed in 563 sample pairs (45.1%) and positive histology in 292 (23.4%), with concordance of 64.0%. The correlation was significant (OR: 3.8, 95% CI: 2.8-5.0). Considering microbiology as the gold standard of infection, the sensitivity of histopathology was 36.1%, specificity was 87.0%, and positive and negative predictive values were 69.5% and 62.4%, respectively.

Table 5 shows the concordance in the subgroup of tissue samples, time from last surgery and microorganisms. Positive culture and positive histology were more closely correlated with early presentation before one month (OR: 9.1, 95% CI: 3.6-23) or three months (OR:7.7, 95% CI: 4.2-14) and with pathogenic microorganisms, such as *S. aureus* (OR: 7.8, 95% CI: 5.2-11.8), *Streptococci* (OR: 7.8, 95% CI: 4-15.2) or Enterobacterales (OR: 7.4, 95% CI: 4.2-13.1). There was no significant correlation with *Candida sp.*

Discussion

All academic societies have agreed to include histopathology in the diagnosis of PJI, but only as a minor criterion [2–7] (see Appendix). Histopathology analysis is not systematically performed by all bone and joint infection teams, and there is often controversy regarding the utility of such practices. For this reason, we evaluated histopathology in the diagnosis of PJI in our unit.

We studied histopathology results from 309 arthroplasty revisions in 181 patients. Concordance of histology with major criteria of PJI was 74.1%. The sensitivity and specificity of

histopathology were 61% and 92% respectively. Consequently, the total number of 'histopathology-culture' sample pairs from the same intraoperative location was large (n = 1,248). Concordance of histology with a positive culture was 64%. The highest correlation was observed for very early infection and for virulent microorganisms, such as *Staphylococcus aureus*, *Streptococci* or Enterobacterales.

Definition of histological infection in PJI is not agreed upon. However, the detection and the quantification of NGs are the core of histological diagnosis. In fact, an inflamed granulation tissue and an inflammatory exudate containing numerous NGs are the most common histopathological findings in infected cases, although the cut-off of NGs varies depending on studies from one to 23 [12–15]. The MSIS and other academic societies continue to use the definition of Feldman *et al* [11,16], with a cut-off of five NGs per HPF in five HPFs at 400x magnification. NGs entrapped in superficial fibrin or adherent to the endothelium or small veins are not correlated with infection, which is a cause of false positive [5]. Given the absence of a consensual histological definition, the interpretation of such difficult analyses requires a pathologist with experience in bone and joint infection. That was the case in our study, as the same pathologist, referent for bone and joint infection, examined all paraffin-embedded sections.

Histological examination can be performed on paraffin-embedded specimens or on frozen sections. Frozen section examination could be useful to help surgeons decide between one or two-stage exchange of implants during surgery [11]. However, Krenn [15] underlined the difficulty of quantifying neutrophils on frozen sections and the need to confirm the results with paraffin examination. Actually, French practices are to give priority to one-stage exchange arthroplasty in cases of joint infection. As a result, frozen sections are less useful. In incomplete

exchange, where it is sometimes difficult to know if there is an infection; in case of positive histology, complete exchange would be required.

In our study, the concordance of positive histology was 74.1% with MSIS major criteria of PJI and 64% with positive culture in the same area (corresponding ORs: 17.2 and 10.8). Considering positive culture as the gold standard of PJI, the sensitivity of positive histology was low (36%), but the specificity was high (86%). High specificity has also been frequently reported in previous studies. Pace *et al* [17] studied frozen sections from 25 synovial specimens, the presence of positive histology showed specificity of 93% and sensitivity of 82% compared with positive culture. In a later study, among 45 patients who had intraoperative frozen section during hip or knee arthroplasty revision [18] specificity was 95% and sensitivity 50%. In a larger population of 136 patients with suspected hip PJI, the specificity and sensitivity of frozen sections in comparison with culture were 87% and 85%, respectively [19]. Tohtz *et al* [20] studied frozen and paraffin sections from 52 hip arthroplasty exchange procedures and reported specificity of 100% and sensitivity of 86.6%. Muller *et al* [21] in two-stage revisions for suspected PJI found high specificity and sensitivity (92% and 95%, respectively). Histology yielded the highest accuracy (0.94) and had the same specificity as intraoperative cultures (92%) for PJI diagnosis in comparison with other parameters (aspiration, CRP, white blood-cell count) [21]. The presence of positive histological specimens could help physicians when all the criteria of PJI are not fulfilled. In our study, PJI was retained by the bone and joint infection team in the absence of MSIS criteria in three cases with positive histology, one with concomitant positive culture with non-virulent microorganisms and two with sterile cultures. This result is rather disappointing considering that it concerned 3 cases out of 38. Other clinical, radiological and biological results helped them in the diagnosis. MSIS in 2018 and, more recently, the European Bone and Joint Society have included new diagnostic tools (see Appendix).

International guidelines recommend using histopathology analysis as a diagnostic tool, but there is high variability in the specimens submitted for histological evaluation. In a study including 69 revisions, Bori *et al* [22] showed that the rate of acute inflammation (defined by five neutrophils per HPF) was higher in periprosthetic interface membranes than in pseudocapsules. False-negative results are mostly due to sampling error. As stated by many authors, multiple samples, including tissue from the periprosthetic interface membrane and neosynovium, may be more effective in detecting focal areas of inflammation [15]. In this study, the majority of the samples was taken from neosynovium and periprosthetic membrane (55.5%), microbiology and histology taken from the same area enabled interpretation of results. Histopathology is of interest for the PJI diagnosis when it is positive, and taking multiple samples in areas of interest can be determinative.

Microbiology is the gold standard for the diagnosis of PJI, as it identifies the offending organism(s) and its (their) antibiotic susceptibility. Some microorganisms causing PJI are highly virulent, such as *S. aureus*, *Streptococci* or Enterobacterales. Other less pathogenic bacteria, such as CoNS or *C. acnes*, are often associated with low-grade infections where tissue alterations could be moderate due to a lack of neutrophil infiltration. Therefore, the histopathology analysis could be negative even in the presence of such an infection. Many examples have been given in previous studies, as in that of Bori *et al* [23], including 38 arthroplasty revisions for a septic cause. In this study, all frozen sections were positive (≥ 5 NGs), except in two cases where infection was due to CoNS. Low-grade infections often have a delayed clinical presentation, and the bacterial load is low. In one study, among 40 hip and knee arthroplasty revisions after arthroplasty procedures performed six to 35 months previously [24], five were considered infected with a negative frozen section (two with negative cultures). In our study, subgroup analysis of acute inflammation showed a high association with virulent

microorganisms (*S. aureus*, OR = 7.8 [5.2-11.8], *Streptococci*, OR = 7.8 [4-15.2] Enterobacterales, OR = 7.4 [4.2-13.1]) and early infection (OR = 7.7 [4.2-14]). In these obvious cases of infection, histology is not relevant. The interest of histology is in chronic infection with CoNS or *C. acnes*, but our study has shown that histology can be falsely negative and therefore not help the physician in making the diagnosis of infection. Low-grade infection remains a challenge for physicians involved in PJI.

This underlines the value of multidisciplinary management in which the histopathologist may have a role to play.

There are several limitations to our study. Although the population was large, it was a retrospective study. Some data were difficult to collect and require careful interpretation. This limitation did not allow us to apply the 2018 MSIS or European Bone and Joint Infection Society (EBJIS) definition for PJI. Many patients referred to our center have a long history of PJI (45% in this study). Therefore, it is difficult to generalize our findings to all populations of patients with PJI. Although the pathologist was trained in bone and infection, there was no second interpretation of histopathological samples by another pathologist.

Conclusion

These results confirmed the value of histopathological examinations as a criterion for PJI diagnosis. The presence of neutrophil granulocytes was better correlated with positive cultures in acute infection and/or infection due to highly virulent bacteria, while caution is needed to interpret the histological results in case of a chronic or a low-virulence microorganism infection. Other diagnostic tools are necessary for such infections.

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Prosthesis	Hip	Knee	Ankle	Shoulder
Patients (n, %)	91	83	3	4
First prosthesis (n, %)	47	49	2	3
Time from the last surgery in months (median, IQR)	9 (2-31)	6 (2-27)	28 (2-37)	6.5 (2-13)
Surgeries (n, %)	144	154	5	6
Retention of implant	9	23	0	1
One-time exchange	64	65	2	3
Two-time exchange	71	66	3	2
Preoperative sample (median, IQR)				
Microbiology	5 (4-6)	5 (4-6)	4 (3-4)	5 (4-7)
Histopathology	4 (3-5)	4 (3-5)	3 (2-4)	4.5 (4-5)

Table 1. Characteristics of prosthetic revision surgeries by location (IQR = interquartile range)

Monomicrobial PJI	N=142
Staphylococcus aureus	34
Staphylococcus epidermidis	48
Staphylococcus lugdunensis	6
Other Coagulase-Negative Staphylococci	9
Streptococcus sp.	14
Enterococcus faecalis	6
Enterobacterales	8
Pseudomonas aeruginosa	6
Cutibacterium acnes	3
Candida sp.	6
Other	2
Polymicrobial PJI	N=28

Table 2. Microbiological results (PJI = prosthetic joint infection)

	All surgeries N=309	With major criteria N=177	Without MSIS diagnosis of PJI* N=127
Sinus tract in communication	53 (17.1%)		
Identical microorganism isolated from ≥ 2 cultures**	170 (55.0%)		
Elevated serum CRP (>10 mg/L)	146 (72.4%) (N=201)	108 (83.1%) (N=130)	38 (53.5%) (N=71)
Any elevated synovial fluid leukocyte count***	37 (56.9%) (N=65)	32 (78.0%) (N=41)	5 (20.8%) (N=24)
Any increased percentage of synovial fluid neutrophils	Missing data		
Purulence surrounding the prosthesis	Missing data		
A single culture with any microorganism	84 (27.2%)		45 (34.1%)
Acute inflammation of the periprosthetic tissue	119 (38.5%)	108 (61.0%)	11 (8.3%)

Table 3. The 2011 Musculoskeletal Infection Society (MSIS) criteria for prosthetic joint infection and description of the 309 studied surgeries (CRP = C-reactive protein)
In bold characters, the major criteria
* Without major criteria and without 4 minor criteria
**Or isolation of a single virulent organism
***Nondefinitive threshold, >3000 cells/mm^3 was determined here

	Se	Sp	PPV	NPV
Acute inflammation in histological examination	61.0	91.7	90.8	63.7
CRP>10 mg/L	83.1	46.5	74.0	60.0
Synovial leukocytes > 3000/mm^3	78.1	79.2	86.5	67.9
One microorganism	22.0	65.9	46.4	38.7

Table 4. Sensibility (Se), Specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for minor MSIS criteria
CRP=C-reactive protein
MSIS=Musculoskeletal Infection Society

		n	Concordance Histopathology/ Microbiology	OR	CI 95%
Sample	Neosynovium / Periprosthetic membrane / Abscess	704	440 (62.5%)	3.7	2.6-5.5
Time from last surgery	≤ 1 month	154	103 (66.9%)	9.1	3.6-23
	≤ 3 months	386	269 (69.7%)	7.7	4.2-14.0
	3-24 months	467	292 (62.5%)	3.4	2.2-5.3
	> 24 months	323	202 (62.5%)	3.1	1.8-5.3
Location of prosthesis	Hip	587	375 (63.9%)	3.8	2.5-5.8
	Knee	619	404 (65.3%)	3.9	2.6-5.9
Positive culture *vs* sterile	*Staphylococcus aureus*	813	665 (81.8%)	7.8	5.2-11.8
	CoNS	935	657 (70.3%)	2.2	1.5-3.1
	Streptococcus sp.	724	617 (85.2%)	7.8	4.0-15.2
	Enterococcus sp.	715	605 (84.6%)	2.3	1.3-6.5
	Enterobacteriaceae	742	629 (84.4%)	7.4	4.2-13.1
	Pseudomonas aeruginosa	703	599 (85.2%)	1.3	0.4-4.7
	Cutibacterium acnes	709	604 (85.2%)	3.3	1.4-8.1
	Candida sp	698	598 (85.7%)	1.2	0.3-5.6

Table 5. Subgroup analysis of concordance of microbiology and histopathology in the same intraoperative sample (OR = Odds ratio; CI 95% = confidence interval of 95%; CoNS = coagulase-negative *Staphylococci*)

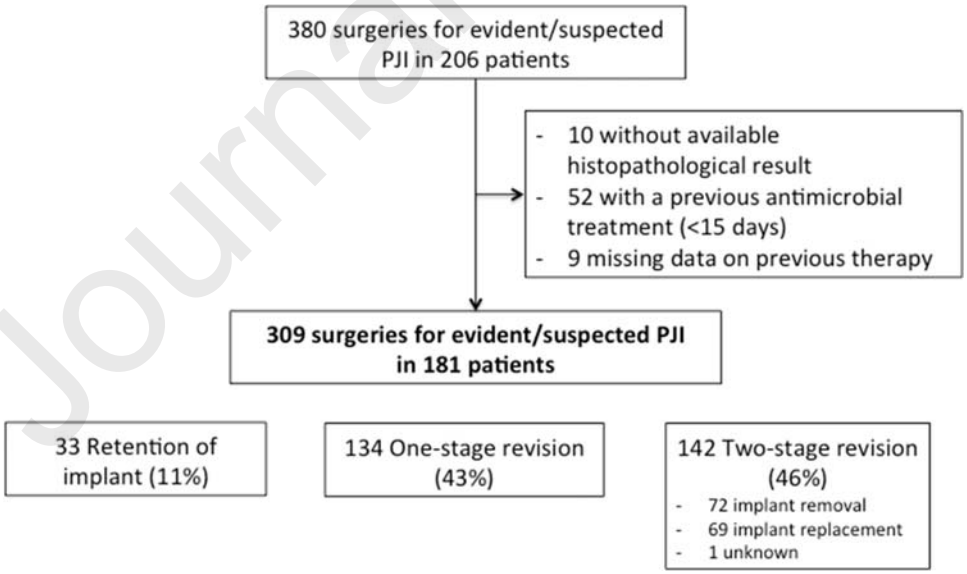

Fig 1 : Study flowchart (PJI=prosthetic joint infection)

	MSIS 2011	MSIS 2018	EBJIS 2019
Major criteria = Infected	*any positive finding*	*any positive finding*	*any positive finding*
	Two positive cultures of the same microorganism	Two positive cultures of the same microorganism	Two positive cultures of the same microorganism*
	Sinus tract with communication to the joint or visualization of the prosthesis	Sinus tract with communication to the joint or visualization of the prosthesis	Sinus tract with communication to the joint or visualization of the prosthesis
			WBC count in the synovial fluid > 3000 cells/µl
			> 80% NGs in the synovial fluid
			Positive Alpha-defensin in the synovial fluid
			Histology: ≥ 5 NGs in ≥ 5 HPF or presence of visible microorganisms
Minor criteria	*4 of the 6 following*	*Preoperative score: ≥6 Infected; 2-5 possibly* *If inconclusive or dry tap, add intraoperative findings: ≥6 Infected; 4-5 Inconclusive*	*Infection likely (2 positive findings)*
Preoperative			- Radiological signs of loosening < 5 years after implantation - Previous wound healing problems - History of recent fever / bacteremia
			Positive WBC scintigraphy
	Elevated CRP or ESR	Elevated CRP or D-dimer (2)	CRP ≥ 10 mg/l
		Elevated ESR (1)	
	Elevated WBC count in the synovial fluid	Elevated WBC count in the synovial fluid or positive leukocyte esterase (3)	WBC count in the synovial fluid]1500-3000] cells/µl
		Positive Alpha-defensin in the synovial fluid (3)	

Intraoperative	Elevated synovial NGs%	Elevated synovial NGs% (2)	Synovial fluid NGs]65-80] %
		Elevated synovial CRP (1)	Positive culture of synovial fluid
	Histology: ≥ 5 NGs in ≥ 5 HPF	Positive histology (3)	Histology: ≥ 5 NGs in 1 HPF
		Purulence around the prosthesis (3)	Purulence around the prosthesis
	Single positive culture	Single positive culture (2)	Single positive culture**

Appendix. Proposed diagnostic criteria for prosthetic joint infection of academic societies (MSIS = Musculoskeletal Infection Society; EBJIS = European Bone and Joint Infection Society; WBC = white blood cells; NG = neutrophil granulocytes; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate)

*if sonication: > 50 CFU/ml of any microorganism

**if sonication: > 1CFU/ml of any organism

Authors' contributions

CF, EB and GG did the conceptualization and wrote the protocol

AGB, PM, GK, GG and AB gave data

CF did the analysis and wrote the original draft

AGB, GG and EB supervised and did the rereading

The authors declare no conflict of interest