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The identification of pathogens associated with periprosthetic joint infection in two-stage revision

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Abstract. – OBJECTIVE: Identification of periprosthetic joint infection (PJI)-related pathogens is crucial to decide what is the correct surgical strategies and the most secure timing to re-implant in case of two-stage revision. The purpose of the present study is to review the literature to identify the features of each exams which are used to identify the pathogens associated with PJI, to evaluate which are the most sensitive and specific and to set up an algorithm to decide when, in the field of two-stage revision, it's the ideal timing to re-implant.

MATERIALS AND METHODS: We did a systematic review of the literature to look for peer-reviewed papers of any evidence level focusing on: (1) Microbiological and molecular exams for identification of PJI-related pathogens. (2) Nuclear imaging methods, which can help in the identification of a PJI. Special attention was focused to analyse which is the sensitivity and specificity of these exams.

RESULTS: Overall, 64 manuscripts met the criteria of the systematic search at point 1 and 7 manuscripts at point 2. Among microbiological and molecular exams, the average of sensitivity and specificity were respectively 65.6% and 94.4% for cultural exams, 74.1% and 95.2% for molecular diagnosis and 86.9% and 96% for MicroDTTect. Among nuclear imaging methods, the average of sensitivity and specificity were respectively 94% and 69 % for three-phase bone scintigraphy and 100% and 62.5% for [18F] Fluoro-2-deoxyglucose-positron emission tomography/computed tomography.

CONCLUSIONS: In two-stage revision after PJI, taking into account the sensitivity and specificity values, just a few microbiological and molecular exams and nuclear imaging methods should be considered in the decision process to re-implant the components.

Key Words:
Periprosthetic joint infection, Two-stage revision, Cultural, Molecular, Nuclear imaging, MicroDTTect.

Introduction

Periprosthetic joint infection (PJI) is a major cause of failure in Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA), although in most national institutes the incidence still remains lower than 2%[1].

PJI-associated revision results in a mortality 5 times greater than in revision for aseptic failure[2], and the cost for a PJI-associated THA revision is 2.8 times greater than aseptic one and 5 times greater than a primary implant.

The economic impact is also a concern for the Healthcare system: in the USA, the overall cost to treat PJI was $566 million in 2009 alone, a number that is projected to reach $1.62 billion in 2020[3]. Obviously, surgery involving multiple steps increases this cost further.

To date, two definitions for the diagnosis of PJI are worldwide accepted, although many have been proposed over the years[4-6]: the IDSA (Infectious Diseases Society of America) and MSIS (Musculoskeletal Infection Society) definitions of PJI, which present a high concordance despite different features[7]. However, despite the lack of an international consensus definition of PJI[8], in this paper, we refer to the MSIS classification system, which is most commonly used by the orthopaedic community.

PJI can be treated by several different medical and surgical strategies. Antimicrobial suppression without surgery and Debridement, Antibiotics, and Implant Retention (DAIR) are the less invasive procedures, because the implant is not removed. Removing the prosthesis can be followed or not by reimplantation, which can be performed either at the time of removal (one-stage revision) or delayed by weeks to months (two-stage revision). Arthrodesis and amputation are the final solutions when other strategies have failed. However, each

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surgical procedure aims to remove all infected tissue and hardware or to decrease the amount of biofilm with postoperative antimicrobial therapy if the prosthetic material is retained.

Background

The two-stage revision, also named two-stage arthroplasty exchange, is currently the most accepted surgical strategy for the treatment of PJI. Success rates for two-stage revision for knee prosthesis infection are about 90% with better outcomes than one-stage revision[9]. For hip arthroplasty infection, reported success rates range from 87 to 100%[10,11].

The main indication of two-stage revision has been in chronic PJI management. However, it is increasingly considered in cases of acute PJI where initial DAIR or one-stage exchange procedures have failed[12] or in immunocompromised host[13]. Resistant organisms as the cause of infection are a bad prognostic factor with higher failure rates in the treatment of PJI[14,15]; some studies suggest that two-stage exchange may be the preferred treatment for highly virulent organisms[16,17]. Another indication may be insufficient soft-tissue coverage, especially if the time for flap development is required; some authors recommend two-stage exchange over a one-stage in case of significant bone loss and soft-tissue compromise[18]. This procedure consists of removal of the implants, meticulous irrigation and debridement, placement of a temporary dynamic (also named articulating) or static antibiotic-impregnated cement spacer and delayed component reimplantation.

The function of antimicrobial-loaded PMMA (PolyMethylMethAcrylate) spacers is of crucial importance. First, they provide a local antimicrobial effect to augment systemic therapy during the time between the first and second stage. Locally presence of loaded spacers allows to reach a higher concentration of antimicrobials at the site of infection than that achievable with systemic therapy, without significant toxicity. Two or more antimicrobials, generally vancomycin, and an aminoglycoside, may be included in a single spacer in order to provide broad-spectrum coverage[19,20].

Secondly, both articulating and static spacers provide mechanical support during the time in which the joint is prosthetic component-free. This preserves proper joint position, prevents muscle contractures, and enhances patient comfort between the first and second stages.

Identification of pathogens related with PJI is crucial to decide what is the correct surgical strategies and the most secure timing to reimplant in case of two-stage revision, but not all the commonly used procedures, devices and tests have the appropriate sensitivity and specificity to reach this aim.

A combination of clinical judgment, aspiration, and serological data can aid the surgeon's decision on the appropriate time for reimplantation[21].

We aimed at reviewing the literature to identify the features of each procedure and device, and testing which are used to identify the pathogens associated with PJI. In this way, we aimed to evaluate which exams are the most sensitive and specific to set up a decisional algorithm about the ideal timing for reimplantation in case of the two-stage revision. We also review the literature to find some imaging methods that could help about this last aspect.

With the term "identification of pathogens" is intended the demonstration of the species of germs which directly causes the PJI.

The exams were evaluated independently by the used Criteria to define PJI.

Materials and Methods

We did a systematic review of the literature, based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, to look for peer-reviewed papers of any evidence level focusing on identification of PJI-related pathogens.

MEDLINE was searched through PubMed with use of the following search strategies:

1. ("prosthetic joint infection" OR periprosthetic joint infection") AND "culture"
2. ("prosthetic joint infection" OR periprosthetic joint infection") AND ("molecular" AND "diagnosis") AND ("polymerase chain reaction" OR "PCR")
3. ("dithiothreitol" OR "microDTTect" OR "DTT") AND ("prosthetic joint infection" OR periprosthetic joint infection")

Only full-text papers published in the English language from January 1, 2000 to January 31, 2018 were included. Abstracts, case reports, letter, reply, comment on, and conference proceedings were excluded in search filters a priori. Furthermore, only studies in which a detailed evaluation of the methods was present, were eligible for inclusion. Special attention was focused to analyse which is the sensitivity and specificity to identify PJI-related pathogens. Studies not reporting sensitivity and specificity values of the exams were excluded. When a study compared sonication or swab or synovial fluid culture versus periprosthetic tissue culture, we reported values referred to

periprosthetic tissue culture. When a study compared different culture media, we reported the one with the highest sensitivity and specificity values. When a study reported a value as a range, the average of the board values was considered. When a study compared the sensitivity and specificity of a culture in chronic versus acute PJI, an average of the values has been made. Studies in animals were excluded. Studies evaluating only a microorganism were excluded. For cultural exams, the sensitivity and specificity were reported regardless of where the specimens were withdrawn.

We also evaluate if there are some imaging methods which can help in the identification of a PJI.

MEDLINE was searched through PubMed with use of the following search strategies:

4. ("prosthetic joint infection" OR periprosthetic joint infection") AND ("nuclear imaging" OR "nuclear method")

Only full-text reviews published in the English language from January 1, 2000 to January 31, 2018 were included. We searched only reviews to detect all the possible nuclear exams in literature useful for our aim, a priori excluding the non-nuclear imaging for the known lack of accuracy in PJI, as depicted in "Discussion" paragraph.

From the analysis of the reviews, three exams appear to be of some relevance in the field of PJI, but with this search criterion, none review focused on sensitivity and specificity of one of these. So that, we decided to extend the search.

MEDLINE was searched again through PubMed with use of the following search strategies:

5. ("prosthetic joint infection" OR "periprosthetic joint infection") AND ("SPECT/CT" OR "SPECT-CT")

Only full-text papers published in the English language from January 1, 2000 to January 31, 2018 were included. For each search at point 4 and 5, special attention was focused to analyse which was the sensitivity and specificity. Studies not considering these items were excluded. In particular, we focused on the sensitivity and specificity of the exams in the decision process for the timing of the reimplant in PJI-related two-stage revision.

All the papers analyzed focused on the ability of the different methods to diagnose PJI, but not on their utility in reimplantation timing in case of two-stage revision. Only two methods seemed to do this. So that, we do a further search through PUBMED with this strategy:

6. "scintigraphy" AND "two-stage revision" AND "infection"
7. ("PET" OR "positron emission tomography") AND "two-stage revision" AND "infection"

For points 6 and 7 only papers published in the English language were included, without using any additional filters. We excluded all papers which not reported sensitivity or specificity of the method.

Results

A total of 300 studies were identified from the keywords search at point 1; a total of 42 studies at point 2; a total of 5 studies at point 3. 283 studies, comprising points 1, 2, and 3, were excluded from review of papers. Overall, 64 manuscripts met the criteria of the systematic search.

The exams and their features which were in detail evaluated in literature to their possible use in identification of pathogens related to PJI are analysed in "Discussion" paragraph. The sensitivity and specificity of those tests were listed for authors and year in Table I, II and III. The average of sensitivity and specificity were respectively 65.6% and 94.4% for cultural exams, 74.1% and 95.2% for molecular diagnosis and 86.9% and 96% for MicroDTTect.

In 7 cases, for cultural exams, the study reported the sensitivity but not the specificity.

Among imaging methods, a total of 22 papers were identified from the keywords search at point 4 and 4 papers at point 5 (a total of 15 papers, of which 11 were just found in the search at point 1). 21 studies, comprising points 4 and 5, were excluded from review of papers. Overall, 5 manuscripts met the criteria of the systematic search.

– Three exams appear to be, for their sensitivity and specificity values (listed for authors and year in Table IV), of a certain utility to help the identification of PJI:

– Three-phase bone scintigraphy with radioactive In-111-labelled leukocytes (average sensitivity and specificity respectively 84.5% and 93.5%).
– SPECT/CT (Single-Photon Emission Computed Tomography/Computed Tomography) (average sensitivity and specificity respectively 91.2% and 83.2%).
– Antigranulocyte Antibody Scintigraphy (LeukoScan) (average sensitivity and specificity respectively 90% and 95%) 18F FDG-PET/CT ([18F] Fluoro-2-deoxyglucose-positron emission tomography/computed tomography) has been excluded for the bro-

Table I. Sensitivity and specificity value for cultural exam from synovial joint aspiration fluid, periprosthetic tissue and sonication fluid.

Authors, year	Sensitivity (%)	Specificity (%)
Morgenstern, 2018[22]	52	/
Lee, 2017[23]	85	90
Rothenberg, 2017[24]	70	90
Van Diek, 2017[25]	68	80
Pohlig, 2017[26]	87.5	100
Sambri, 2017[27]	94.4	100
Liu, 2017[28]	79	95
Peel, 2016[29]	98	/
Ahmad, 2016[30]	70	89
Rak, 2016[31]	76	93
Park, 2016[32]	61.5	95.5
Peel, 2016[33]	90.2	99.5
Lazureanu, 2015[34]	0	93.14
Fernández-Sampedro, 2015[35]	66.7	100
Alijanipour, 2015[36]	82	32
Nodzo, 2015[37]	73	95
Shen, 2015[38]	64	98
Jordan, 2015[39]	25	98
Niedźwiadek, 2014[40]	69	/
Dilisio, 2014[41]	100	100
Scorzolini, 2014[42]	34.1	/
Ryu, 2014[43]	68.8	100
Jordan, 2014[44]	32	99
Minassian, 2014[45]	82.3	98.8
Portillo, 2014[46]	61	100
Smith, 2014[47]	19	88
Cross, 2014[48]	41	100
Miyamae, 2013[49]	71	87
Evangelopoulos, 2013[50]	47.1	/
Qu, 2013[51]	72	95
Janz, 2013[52]	52	100
Drago, 2013[53]	71.4	76.5
Cazanave, 2013[54]	70.1	97.9
Aggarwal, 2013[55]	93	98
Janz, 2013[56]	87	100
Portillo, 2012[57]	67	98
Gomez, 2012[58]	70.4	98.7
Larsen, 2012[59]	79.5	/
Corona, 2012[60]	82	100
Vergidis, 2011[61]	55	93
Hughes, 2011[62]	87	98.5
Holinka, 2011[63]	61.1	/
Bergin, 2011[64]	71	96
Font-Vizcarra, 2010[65]	85	100
Meermans, 2010[66]	90	100
Tohtz, 2010[67]	86.6	100
Piper, 2009[68]	54.5	95.1
Gallo, 2008[69]	44	94
Fihman, 2007[70]	53.8	85.7
Trampuz, 2007[71]	60.8	98.8
Bori, 2007[72]	28.5	100
Mikkelsen, 2006[73]	46	100

ad variability of sensitivity and specificity values; the other exams demonstrated more reproducible values.

Table II. Sensitivity and specificity value for molecular diagnosis.

Authors, year	Sensitivity (%)	Specificity
Morgenstern, 2018[22]	60	89
Rak, 2016[31]	95	97
Melendez, 2016[74]	55.6	91.8
Bémer, 2014[75]	73.3	95.5
Qu, 2013[76]	86	91
Cazanave, 2013[54]	77.1	97.9
Rak, 2013[77]	75	94.1
Marìn, 2012[78]	94	100
Bergin, 2010[64]	71	100
Fhiman, 2007[70]	53.8	95.2

Table III. Sensitivity and specificity value for MicroDTTect.

Authors, year (%)	Sensitivity (%)	Specificity (%)
De Vecchi, 2016[79]	88	97.8
Drago, 2013[53]	85.7	94.1

At point 6 a total of 4 papers were identified from the keywords search, but only 2 met the criteria of the systematic search. At point 7 a total of 2 papers were identified from the keywords search, but only 1 met the criteria of the systematic search, and this paper is the same of one of the papers at point 6. Two exams appeared to be useful in the decision process for the timing of the reimplant in PJI-related two-stage revision:

– Three-phase bone scintigraphy.
– 18F FDG-PET/CT.

In Table V, we reported the sensitivity and specificity values, positive predictive value (%) and negative predictive value (%) of these studies listed for authors and year.

With all these information, we created a flowchart of a possible decision process of when is the ideal timing to proceed with the reimplantation in two-stage revision (Figure 1).

Discussion

The identification of pathogens can be directly obtained with molecular diagnosis or with a cultural exam. The main point for the cultural exam is whence the specimen to test is obtained:

– Swabs
– Synovial fluid directly aspirated from the infected joint
– Periprosthetic tissue biopsy
– Sonicate fluid of removed prosthetic components

Table IV. Sensitivity and specificity value for nuclear imaging.

	Authors, year	Sensitivity (%)	Specificity (%)
SPECT/CT	Kim, 201480	93.3	93.3
	Graute, 201081	89	73
Three-phase bone scintigraphy with In-111-labeled leukocytes	Verberne, 201682	69	96
	Love, 200483	100	91
LeukoScan	Verberne, 201784	90	95

Table V. Sensitivity and specificity value, positive predictive value (%) and negative predictive value (%) for nuclear imaging useful in the decision process for the timing to re-implant.

	Authors, year	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Three-phase bone scintigraphy	Ikeuchi, 201385	94	69	80	90
18F FDG-PET/CT	Chen, 201086	100	62.5	/	100

– Fluid obtained from Dithiothreitol (DTT) solution devices

Molecular Diagnosis

Polymerase Chain Reaction (PCR) technology has the theoretical advantage of a rapid response time and higher sensitivity than conventional microbiological methods[64,69,87,88]. In particular, this method is not affected by a previous use of antimicrobials.

Nowadays, Real Time-PCR (RT-PCR) is the most used technique. It allows the detection of PCR

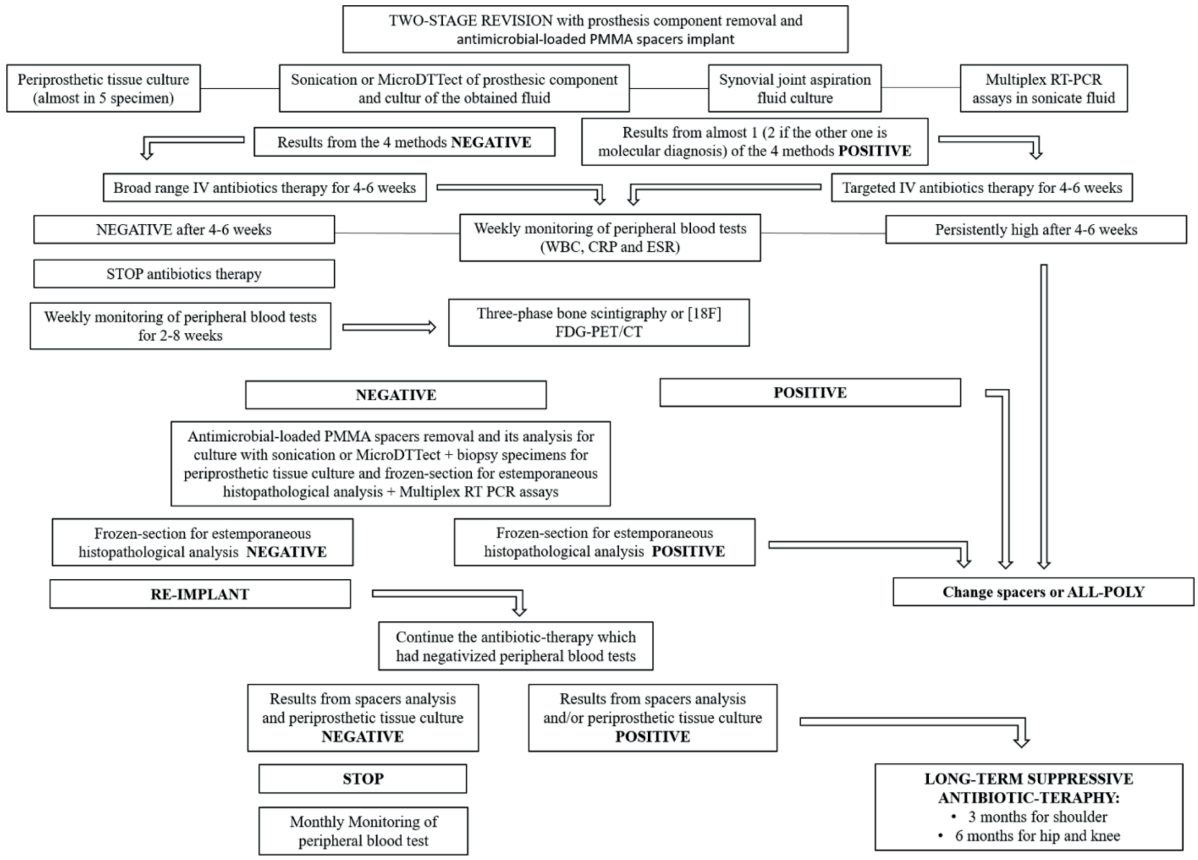

Figure 1. Proposal of an algorithm to decide when to re-implant in two-stage revision

amplification during the early phases of the reaction. This provides a distinct advantage over traditional PCR, which uses Agarose gels for detection at the final phase or end-point of the reaction.

Targeting the gene encoding 16S ribosomal RNA (commonly named broad-range PCR or 16S PCR), PCR identifies nucleic acid sequences conserved across many bacterial species. As such, it may permit the identification of bacteria never previously associated to cause PJI.

One of the limits of standard PCR is the rate of false positives, which some studies using 16S PCR reported to be high[88]. This rate decreases if RT-PCR is used and the analysis conducted in sonicate fluid[58]. Sensitivity is lower and with variable values in the study with PCR on synovial fluid[69,87,88] than on sonicate fluid[58].

The most relevant concern is polymicrobial infection, which may cause a band overlap confirming the presence of infection without identification of the species. This would require an additional sequencing step in order to analyse the DNA of each species.

Conversely, multiplex or multi assay PCR is limited to targeted primers of pathogens that are most frequently associated to PJI. This allows to have a method that, finding only what it seeks, is higher specific. Results are available within 3-5 hours, making the procedure very quick. Cazanave et al[54] designed a panel of 10 real-time PCR assays specifically targeting the bacteria that most frequently cause PJI. This large study, involving 434 patients (144 with PJIs), found that sonicate fluid PCR was more sensitive (77%) than tissue culture (70%) but not sonicate fluid culture (73%), compared to a non-microbiological definition of PJI. Conversely, the specificity of this PCR panel was high (98%), suggesting that if aseptic failure is due to indolent infections, as other investigators have suggested[89], it is not caused by organisms that commonly cause overt PJI. For the patients receiving antibiotics in the 2 weeks prior to surgery, PCR was 88% sensitive, compared to 70% sensitivity for tissue or sonicate fluid culture, suggesting a situation in which this technology may be particularly advantageous. However, this technology doesn't allow for mycotic search.

The incoming of the Ibis T500 Universal Biosensor, which combines broad-range PCR with high-performance electrospray ionization mass spectrometry (ESI-MS), could largely improve some of these issues. This system outperforms standard PCR and allows to detect bacteria, viruses, fungi, and protozoa[90]; however, it retains the high false-positive rate of conventional PCR[91]. In their study, Jacovides et al[92] correctly identified with this technology the pathogen in 17 of 18 culture-positive PJI cases. However, a very poor specificity was observed, with one or more organisms being identified in 50 of 57 non-infectious revisions and 5 of 7 primary arthroplasties, significantly limiting the application of this technology. Given these data, PCR ESI-MS may be useful in the future in selected cases of PJI, e.g., in diagnosing culture-negative suspected PJI.

Nowadays, given the limitations of commercially available multiplex PCR assays designed for other purposes, multiplex PCR assays in sonicate fluid that includes the most likely organisms causing PJI should be used for PJI diagnosis.

The biggest limitation of this technology is that doesn't allow to get an antibiotic susceptibility test; therefore, even when positive, another exam must be necessarily performed to administrate a targeted antibiotic therapy.

Culture Exam

Swabs

Cultures obtained by using swabs have a limited role in the pathogen identification in PJI.

While the presence of a sinus tract is considered definitive evidence of PJI[4,5], swab culture of the drainage from the sinus tract is neither sensitive nor specific for the microbiological detection of PJI.

Tetreault et al[93] recently evaluated the utility of sinus tract swab culture in patients with knee or hip arthroplasty and a draining wound. Among the patients diagnosed with a PJI based on MSIS criteria, the concordance between superficial sinus tract culture and operative tissue culture was 53%, with numerically lower concordance in the acute PJI group versus chronic PJI.

Intraoperative cultures obtained via swabs are less accurate than tissue cultures. Aggarwal et al[55] compared intraoperative swabs with tissue samples from patients undergoing revision arthroplasty and found that swab cultures obtained from the same site as tissue samples had sensitivity and specificity of 70 and 89%, respectively, compared to 93 and 98%, respectively, for tissue cultures. Another study reported a similar sensitivity value[65]. The sensitivity of swab culture was particularly poor for patients with chronic PJI, at only 40%.

Synovial fluid directly aspirated from the infected joint

As recommended for swabs, fluid aspiration from draining wound or sinus tract after hip or

knee arthroplasty should not be obtained[93], because of the evidence that commensal skin bacteria are commonly identified in these superficial cultures, but are not considered pathogenic unless isolated from a sterilely obtained joint aspirate or intraoperative culture. In this way, superficial cultures could mislead the diagnosis and treatment of intra-articular pathology. Specifically, they can lead to a diagnosis of deep infection within the joint space when it is not present, leading to unnecessary surgical intervention.

Aspirated fluid can be either inoculated into blood culture bottles at the time of collection or transported to the microbiology laboratory and inoculated onto solid and/or liquid media. It's recommended the use of aerobic and anaerobic blood culture bottles inoculated in the procedure suite. This method has the advantages of increased pathogen recovery and decreased risk of contamination when used with native joint synovial fluid[94], in contrast with the low sensitivities (50%) using of only solid or liquid media[95-97].

In several studies, the sensitivity was consistently high, from 86 to 87%, with a specificity ranging from 95 to 100%[65,98], with higher sensitivity for acute (91%) than for chronic (79%) PJI, probably due to the difference in the load of microorganisms or the infecting pathogens[65]. In studies with lower sensitivity value, patients had received antibiotics in the 2 weeks prior to aspiration[54].

Periprosthetic Tissue Biopsy

First of all, obtaining only a single tissue specimen for culture gives a low sensitivity and lead difficulty in interpreting potential contamination with low virulence microorganisms, and should be avoided, as Kamme and Lindberg[99] recognized over 30 years ago, underlined that pathogens could be distinguished from contaminants when five tissue specimens were obtained.

Several studies evaluated what could be the ideal number of specimens to withdraw and the ideal threshold of specimens yielding an indistinguishable microorganism. The sensitivity values ranged from 65% when 5 or 6 number of specimens were chosen and 3 or more specimens yielding an indistinguishable germs were fixed for ideal cut-off[100], to 80% (and a specificity of 97%) when a mean of 4 samples per patient (range, 1 to 7) were withdrawn with isolation of the same organism from three or more cultures[101]. More recently a threshold of two specimens with phenotypically identical organisms demonstrate a good sensitivity[71,102] and this has been incorporated into PJI consensus documents[4,5,8].

When virulent organisms (such as *S. aureus*, *beta-haemolytic Streptococci, or aerobic Gram-negative Bacilli*) are isolated also in a single positive culture, this must be taken in consideration especially when the same organism is found in a different specimen type, such as synovial or sonicate fluid.

About the specific media used for culture, using cooked meat broth (83%) or blood culture bottles (87%) was more sensitive than culture using anaerobic broth (57%) or solid-agar plates (39%). Specificity was 97 to 100% for each medium type[62].

Some studies also evaluate thioglycolate broth with meaningful sensitivity and specificity values[71,101].

Traditionally, aerobic cultures are incubated for up to 4 days, and anaerobic cultures are incubated for up to 7 days; incubation beyond these points is thought to increase the number of contaminants. Recently, some authors[102,103] suggested that periprosthetic tissue should be cultured for 14 days. However, the optimal duration of incubation for periprosthetic tissue culture is of considerable debate, particularly for isolation of *P. acnes*, primarily found in patients undergoing revision of shoulder arthroplasty. Some authors[103] suggested that both aerobic and anaerobic cultures should be incubated for 13 days. Other authors[104] didn't find an increase in detection of *P. acnes* infections when using anaerobic blood agar and anaerobic thioglycolate broth incubated for 14 compared to 7 days; they also suggested a certain advantage of thioglycolate broth in this setting.

Sonicate fluid of removed prosthetic components

Sonication is a method to dislodge biofilm and the associated bacteria from the surface of the implant. Low-frequency ultrasound waves pass through liquid surrounding the prosthesis, creating areas of high and low pressure. Microscopic bubbles formed during the low-pressure stage, collapse during the high-pressure stage, releasing energy and liberating bacteria from the surface of the implant. The fluid surrounding the implant can then be submitted for culture or analysed by culture-independent methods to detect bacteria[105].

The optimal threshold for determining significant bacterial growth is debated. Without the use of a centrifugation (or vortex) phase for the concentration of the fluid, the optimal threshold is 2-10 CFU per millilitre (considering 10 as a threshold there is a decrease in sensitivity at 79% but an increase in the specificity of 99%)[71]. Using a

100-fold concentration step the threshold is 200 CFU per millilitre[68].

The type of bacteria identified when considering a cut-off for significant growth should also be taken into account: the presence of 10 CFU per millilitre of *S. aureus* or a member of *Enterobacteriaceae* should be considered with minor probability a contaminant rather than finding the same amount of *Coagulase-Negative Staphylococci or Propionibacterium species*.

This technique, with a vortex phase, was particularly useful for those patients who took antimicrobial agents in the two weeks prior to surgery, for whom the sensitivity of the sonicated fluid is 75%, compared to 45% of the tissue culture[63].

Using solid culture media is better than liquid media because it allows semi-quantitative analysis to differentiate pathogens from contaminants. Studies that used a solid container to process prostheses found specificity values of 81-100%[61,106-108] compared to 43-87% of studies that used a bag[109,110].

Sensitivity to sonication of shoulder prosthesis (66.7%) may be lower than that for hip or knee prostheses (72.9-78.5%), on studies performed using nearly identical sonication protocols[54,68]. Using vortexing alone in laboratories that do not have sonication available and setting a cut-off to 1 CFU per millilitre results in levels of sensitivity and specificity similar to sonication plus vortexing[106].

Further data are necessary on the role of sonication of the PMMA spacer at the second stage of a two-stage arthroplasty exchange[111,112].

Fluid obtained from Dithiothreitol solution devices

Dithiothreitol is a sulfhydryl compound (empirical formula $C_4H_{10}O_2S_2$, MW 154.2) which is routinely used in clinical microbiology for liquefying specimens from the respiratory tract. DTT is characterized by low toxicity, easy to use since it does not require special precautions, relatively low costs. Sulfhydryl compounds reduce disulphide bounds between polysaccharides and neighbouring proteins, and interfere with biofilm formation. For this reason, this solution is able to detach bacteria from a biofilm on orthopaedic devices with comparable or even higher yields than sonication and periprosthetic tissue culture[53,113].

The DTT solution devices are a closed system which allows intra-operative microbiological samples retrieval with lower risks of contamination in clinical practice. Samples were put into containers that are sturdy, unpeaceable, heat-sealable and equipped with a mini grip and adhesive seal for a watertight closure chamber in PVC (polyvinyl chloride).

Sambri et al[114] found no difference in sensitivity between DTT and sonication for the detection of PJI, and both of those tests were more sensitive than standard tissue cultures. Among patients in whom infection was not suspected before surgery, the sensitivity of DTT was greater than that for sonication and cultures on tissue samples (100% *vs.* 70% and 50%; $p < 0.001$). Among patients in whom infection was suspected before surgery, the sensitivity of DTT and sonication were not greater than standard cultures (89% and 94% *vs.* 86%).

De Vecchi et al[79] compared microbial growth in periprosthetic tissue samples collected from the same site and randomly allocated to DTT or saline treatment. They found concordance between the two methods in the 85.7% of cases. Sensitivity was 88.0% for dithiothreitol and 72.0% for saline. Specificity was 97.8% and 91.1% for dithiothreitol and saline, respectively.

In the two-stage revision, the delayed reimplantation after 4-6 weeks of intravenous antimicrobial therapy and an antibiotic-free period of 2-8 weeks has been highly successful[115,116]. Most panel members would use 6 weeks of therapy for more virulent organisms such as *S. aureus*[117,118].

The timing to reimplant is fundamental. The peripheral blood tests with evaluation of white blood cells (WBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, are worldwide accepted as an excellent predictor of the absence of infection, when normal and when used in combination[119] and can guide the ideal timing to withdraw the antibiotics.

Biopsy specimen for frozen-section histopathological analysis are also fundamental in this phase, with results being available within 30 min, compared to one or more days for permanent histopathology[120]. A recent meta-analysis[121] of 26 studies involving > 3,000 patients (796 PJIs) found that the presence of acute inflammation provided a high positive likelihood ratio of 12. Acute inflammation is defined as the presence of at least 5 neutrophils per high-powered field, in at least 5 separate microscopic fields[122,123] as reported in the recent consensus definitions for PJI[5].

The identification of pathogens must be done intraoperatively at the moment of removal of components and secondly at the time of the reimplantation with a culture exam from the periprosthetic tissue as gold standard, from the culture of synovial joint aspiration fluid, from molecular analysis, and from prosthesis component sonication fluid or DTT fluid.

In the diagnosis of PJI, we analyzed only nuclear methods cause the lack of evidence in sensitivity and specificity of standard and advanced imaging. However, when we looked to the decision process to reimplant in two-stage revision, only two exams seem to have a certain utility, as mentioned above.

Standard and advanced Imaging

The literature points out the lack of accuracy of these technologies in the diagnosis of PJI.

Radiographs

Radiographs are an integral part of evaluating patients with a painful total joint arthroplasty because they may show a periprosthetic fracture, obvious implant loosening, or a dislocation of the joint. However, radiograph results are generally normal in the presence of infection[124].

Some radiographic findings could suggest a PJI but their sensitivity and specificity are low[4,125]:

- focal osteolysis, as indicated by an expanded radiolucency band (> 2 mm) at the metal-bone or cement-bone interface
- detachment of components, particularly fast and aggressive, typical of the infection (*vs.* the slow progression of aseptic loosening)
- breakages in the context of cement
- sub-periosteal reaction

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

They do not have a place in the routine diagnostic evaluation of PJIs, although some authors found that detection of joint distention upon CT imaging was highly sensitive (83%) and specific (96%) for suspected hip arthroplasty infection[126]. Artefacts related to the presence of metal preclude reliable image interpretation and even the current artefact reduction software used in MRI are largely unable to improve the problem adequately[125,127,128].

Ultrasonography

In the diagnosis of PJI its usefulness for a significant accumulation of local liquids that does not make the images clear. It could be useful to guide joint aspiration in some cases[129].

Nuclear Imaging

[18F]Fluoro-2-deoxyglucose Positron Emission Tomography (FDG-PET)

Kwee et al[130] found sensitivity and specificity values of 82.1 and 86.6%, respectively, for the diagnosis of PJI, emphasizing that this is a high-cost technique. However, in patients with orthopaedic implant infections, sensitivity varies widely from 28% to 91% and specificity from 9% to 97%. This variation in FDG-PET performance in orthopaedic implant infections depends largely on the use of different criteria to diagnose infection. Further studies are needed because the present data regarding accuracy are conflicting[125,131,132].

Conversely, Chen et al[86] evaluated the potential role of [18F] FDG-PET/CT to identify latent infections at the site of an interim hip spacer after resection arthroplasty for hip prosthesis infection, finding 100% sensitivity and 100% negative predictive value for detection of latent infection. They concluded that the high negative predictive value of PET/CT scans is useful to rule out infections in patients with persistently elevated CRP levels and might serve as an auxiliary tool to exclude latent infections in patients posing a clinical diagnostic dilemma.

In addition, Huang et al[133] recently reported that FDG-PET was a feasible tool to help in detecting infection around antibiotic-loaded cement spacers.

Although PET is a highly effective procedure for detecting infection around the prosthesis and cement spacers, its limitations are the restricted availability and the costs.

Three-phase Bone Scintigraphy (TPBS) with or without Radioactive In-111-Labelled Leukocytes

Three-phase bone scintigraphy uses a radioactive isotope which is attached to a compound that preferentially collects in bone. This compound will accumulate in areas of high metabolic activity and emits gamma rays that can be detected by a gamma camera. After the injection of the radioactive compound, the intensity of uptake is measured at three different time points: immediate, at 15 min and at 2 to 4h. These timings correspond to blood flow, blood pool, and late pool, respectively. Captation at the blood pool and late time points suggests PJI[134].

The majority of PJIs occurs in the first year or two after implantation, but asymptomatic patients frequently have uptake detected by delayed-phase imaging in this time period[135], leading to a lack of specificity, reportedly as low as 18% by some authors[136]. Therefore, TPBS may be more useful for PJI occurring late after arthroplasty, with increased uptake at both the second and third phases provided sensitivity and specificity of 68 and 76%, respectively, as reported by some authors[137].

Sensitivity and specificity could increase with use of radioactive In-111-labelled leukocytes, with images being obtained 24 h later. A positive scan is typically considered when there is uptake on the labelled leukocyte image, with absent or decreased uptake at the same location on the late-phase bone scan. A late-phase bone scan combined with a 111In leukocyte scan has sensitivity value ranging from 64%-100% and specificity value ranging from 70% to 91% according to different studies[138-140].

Scintigraphy yields a slightly lower accuracy, but excels in simplicity and cost-effectiveness[141].

Ikeuchi et al[85] evaluated TPBS as a diagnostic test for the detection of residual infection around the antibiotic-loaded cement spacer in patients waiting for the second-stage revision hip or knee arthroplasty. They found a positive and negative predictive value of 80% and 90%, respectively, with a diagnostic sensitivity of 94% and a specificity of 69%, concluding that, because FDG-PET is not yet common, three-phase bone scintigraphy has an important role in the diagnosis of residual infection around the prosthesis and cement spacers.

Single-Photon Emission Computed Tomography/Computed Tomography (SPECT/CT)

Scintigraphy with SPECT imaging has the advantage of showing the metabolic activity of the bone surrounding the prosthesis and is less prone than MRI to image degradation by artefacts from metalwork. In SPECT/CT the SPECT gamma scanner may be built to operate with a conventional CT scanner, with co-registration of images; this allows the location of tissues which may be seen on SPECT scintigraphy, but are difficult to locate precisely with regard to other anatomical structures.

Joint and bone infection with or without a prosthesis component has some particular features with this technology, that allow also to distinguish PJI from other pathologies (periprosthetic fracture, aseptic loosening): irregular periprosthetic radiolucencies, periosteal reaction, prolonged intense activity on dynamic and blood-pool phase of bone scintigraphy, circumferential increased uptake around the prosthesis on delayed SPECT, soft-tissue changes: joint distension, fluid-filled bursae, surrounding collections in muscles[142].

Filippi and Schillaci[143] investigated SPECT/CT imaging with ^{99m}Tc-WBC for diagnosis of metallic implant-associated infection. Sensitivity and specificity were 100%. Combining 2 different radiopharmaceuticals or adding CT allow to reach high specificity in diagnosing infection in patients with suspected PJI[144].

Anti-granulocyte Antibody Scintigraphy (LeukoScan)

Several peptides and anti-granulocyte antibodies/antibody fragments are used as *in vivo* methods of labeling leukocytes. One method makes use of a murine monoclonal antibody fragment of the IgG1 class that binds to normal cross-reactive antigen-90 present on leukocytes (LeukoScan). Sensitivity and specificity of this agent range from 76% to 100% and from 67% to 100%, respectively[145].

Rubello et al[146] reported 94% sensitivity for both early and delayed imaging, whereas specificity was 71% for early imaging and 83% for early and delayed imaging approach. At semi-quantitative ROI analysis, sensitivity remained 94%, whereas specificity rose slightly to 73% for early imaging and to 90% for early and delayed imaging combined.

Conclusions

In the two-stage revision, the delayed reimplantation after 4-6 weeks of intravenous antimicrobial therapy and an antibiotic-free period of 2-8 weeks has been highly successful.

Reviewing the literature and analyzing the sensitivity and specificity of the exams which allow the identification of pathogens, we proposed an algorithm to lead the decision process to reimplant the components in two-stage revision after PJI.

Multiplex RT-PCR assays should be used for identification of pathogens related to PJI. It has to be conducted on sonicate fluid and include the most likely organisms causing PJI, Collection of swabs for culture is not recommended.

Synovial fluid should be inoculated directly into blood culture bottles to improve their accuracy in identification of pathogens.

Submission of single periprosthetic tissue specimens for culture is not recommended. Nowadays demonstration of two phenotypically identical organisms of 5 specimens is recommended as gold standard. Culture using aerobic and anaerobic conditions should be performed in all cases. The optimal duration of culture is unclear but likely depends in part on the medium that is used and not just on the incubation period.

The culture of samples obtained by sonication of the removed prosthesis has been shown to be more sensitive than conventional tissue cultures, especially in patients treated with antibiotics be-

fore surgery. However, some limitations of this method have been highlighted, such as the necessity for dedicated laboratory tools and the intrinsic risk of contamination.

Cultures from DTT fluid, obtained from a closed system device, bypass the risk of contamination and should be considered for detection of PJI-related pathogens. Together with other criteria, it should be considered especially in settings where the infection is not suspected before revision surgery.

Finally, non-nuclear imaging has a lack of accuracy, so that it is non-recommended. Among nuclear methods in the diagnosis of PJI, [18F] FDG-PET/CT is not recommended for the high cost of technique and for the broad variability of sensitivity and specificity values. SPECT/CT, LeukoScan, and three-phase bone scintigraphy with In-111-labelled leukocytes must be considered in the diagnosis of PJI, in Healthcare Center where these technologies are available, for reproducible values of sensitivity and specificity.

However, in the decision process of the reimplant, only [18F] FDG-PET/CT and TPBS may play a role.

Conflict of Interest

Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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