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Are Accuracy Studies for Periprosthetic Joint Infection Diagnosis Inherently Flawed? And What to Do with Schrödinger's Hips? A Prospective Analysis of the Alpha Defensin Lateral-Flow Test in Chronic Painful Hip Arthroplasties

Jesse W.P. Kuiper, MD*,†, Steven J. Verberne, MD*, Pim W. van Egmond, MD†, Karin Slot, RN*, Olivier P.P. Temmerman, MD, PhD*, Constantijn J. Vos, MD*

*Department of Orthopedic Surgery, Noordwest Hospital Group, Alkmaar, The Netherlands**
Department of Orthopedic Surgery, Catharina Hospital, Eindhoven, The Netherlands†
Department of Orthopedic Surgery, Elisabeth-TweeSteden Hospital, Tilburg, The Netherlands†

Purpose: The most recent diagnostic criteria for periprosthetic joint infection (PJI) include the use of the alpha-defensin (AD) lateral-flow (LF) test, but hip and knee arthroplasties were usually combined in previous studies. This prospective study was designed to examine the accuracy of the AD-LF test for diagnosis of PJI in chronic painful total hip arthroplasties (THA).

Materials and Methods: Patients with chronic painful hip arthroplasties were prospectively enrolled between March 2018 and May 2020. Exclusion criteria included acute PJI or an insufficient amount of synovial fluid. The modified Musculoskeletal Infection Society (MSIS) criteria were primarily used for PJI diagnosis. Fifty-seven patients were included in the analysis group. Revision surgery was not performed in 38 patients, for different reasons (clinical group); these patients remain "Schrödinger's hips": in such cases PJI cannot be excluded nor confirmed until you "open the box".

Results: The result of the AD-LF test was positive in nine patients and negative in 48 patients. Six patients were diagnosed with PJI. AD-LF sensitivity (MSIS criteria) was 83% (95% confidence interval [CI] 36-100%) and specificity was 92% (95% CI 81-98%). The positive and negative predictive value were 56% and 98%, respectively.

Conclusion: The AD test is useful in addition to the existing arsenal of diagnostic tools, and can be helpful in the

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Address reprint request to
Jesse W.P. Kuiper, MD
(https://orcid.org/0000-0002-4173-4786)
Department of Orthopedic Surgery, Catharina Hospital, Eindhoven, The Netherlands

Jesse W.P. Kuiper's current affiliation:
Department of Orthopedic Surgery, Martini Hospital, van Swietenplein 1, Groningen 9728 NT, The Netherlands
TEL: +31-50-5243970 FAX: +31-50-5245989
E-mail: jwp.kuiper@gmail.com

decision-making process. Not all patients with chronical painful THA will undergo revision surgery. Consequently, in order to determine the reliable diagnostic accuracy of this test, future PJI diagnostic studies should include a second arm of "Schrödinger's hips".

Key Words: Hip, Arthroplasty, Prosthesis-related infections, Diagnosis, Alpha-defensin

INTRODUCTION

Periprosthetic joint infection (PJI), one of the most severe complications after arthroplasty, has a significant impact on the patient and on health care costs[1,2]. Since strategies for treatment of septic prosthetic failure differ considerably from treatments for other causes of arthroplasty failure, an accurate and prompt diagnosis of PJI is of the utmost importance.

PJI cannot be confirmed or excluded based on the result of a single diagnostic test. Several definitions have been proposed in recent years[1,3-6]; of which the modified MSIS criteria, which include two major and several minor sub-criteria, are the most commonly used definition[5] (Supplementary Table 1). The modified 2018 International Consensus Meeting (ICM) (Supplementary Table 2) and European Bone and Joint Infection Society (EBJIS) 2021 criteria (Supplementary Fig. 1), which were recently published, include alpha-defensin (AD), an antimicrobial peptide released by neutrophils in response to pathogens[7]. Two different AD tests are available: the ELISA test, which requires performance of analysis in a laboratory, and the lateral-flow (LF) test, which has the practical advantages of providing a result within 10 minutes and that the analysis can be performed virtually anywhere[7]. Differences in diagnostic accuracies between various joints have been reported[7,8]; a recent meta-analysis reported sensitivity and specificity for THA separate from TKA: pooled sensitivity for THA PJI diagnosis using the LF test was 80%, and specificity was 92%, slightly lower than its accuracy for TKA (87% and 96%, respectively)[7].

No previous prospective study investigating the diagnostic accuracy of the AD-LF test for diagnosis of PJI exclusively in chronic painful hip arthroplasties has been reported in the literature. The SWAG study (Synovasure and White blood cell count after Aspiration compared to the Gold standard) was designed for prospective evaluation of the diagnostic performance of AD-LF testing in this challenging (and heterogenous) group of patients. The aim of the study was to provide answers to the following questions:

1) What is the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the AD-LF test for diagnosis of PJI for chronic painful THA?
2) Which subgroups in which AD-LF testing is more (or less) accurate (e.g., metallosis) can be identified?

MATERIALS AND METHODS

This single center prospective cohort study was conducted in a large secondary teaching hospital and PJI referral center. Approval for the study was granted by the ethics committee of Noordwest Hospital Group in February 2018 (No. L-018-009) and the informed consent was waived by the ethics committee.

Patients (range, 18-99 years) who underwent joint aspiration as part of the diagnostic work-up for evaluation of painful or poorly functioning total hip arthroplasty (THA) between March 2018 and May 2020 at Noordwest Hospital Group were included in a prospective database. A total of 151 consecutive patients underwent joint aspiration during this period. Exclusion criteria for this study were as follows: suspicion of an acute PJI (joint aspiration performed within three months of index surgery), insufficient amount of fluid for AD testing (dry tap, <1 mL), and aspiration performed after resection arthroplasty. A priori, antibiotic use and suspected metallosis were not regarded as exclusion criteria. Data regarding aspirations performed for painful hip hemi-arthroplasties (HHA) were collected separately. The modified MSIS criteria were used to define PJI[5]. For the purpose of comparison, the modified 2018 ICM criteria[6] and EBJIS criteria were also described[9].

Aspiration of the hip was performed in the operating room under sterile conditions using fluoroscopy. A (temporary) diagnosis was then made, and patients were selected for aseptic revision, septic two-stage revision, wait-and-see policy, or antibiotic suppression therapy. Two-stage revision was performed in cases where there was suspicion of PJI. In cases where the results indicated aseptic pathology, one-stage revision was performed or a wait-and-see policy was

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used in subclinical or improving patients. Antibiotic suppression therapy was considered in high-risk patients in terms of substantial co-morbidities with suspicion or evident PJI. Six tissue cultures were collected during performance of revisions surgery. Samples were cultured for at least 14 days.

The patient's history, clinical findings, laboratory tests including serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and results of synovial tests from joint aspiration were documented. The AD-LF test (Synovasure; Zimmer Biomet, Warsaw, IN, USA) was performed according to manufacturer guidelines: after aspiration, the synovial fluid was added to the sample cup, and the microsafe tube was placed horizontally in the cup. Once the fluid had reached the black line on the tube, the contents were transferred to the pre-filled dilution bottle. After mixing, three drops of fluid were dispensed on the lateral flow device, and the results were read after 10 minutes. When a sufficient amount of synovial fluid could be obtained, the remaining fluid was used for culture in blood culture bottles (aerobic and anaerobic), WBC count and polymorphonuclear neutrophil percentage (PMN%), and leukocyte esterase (LE) dipstick testing.

Calculation of sensitivity, specificity, PPV, and NPV of the AD-LF test was performed in the group of patients who underwent revision surgery. Except for age, the scale variables were described using the median and the range regarding a non-normal distribution measured using the one-sample Kolmogorov–Smirnov test. 95% Confidence intervals (CI) were calculated and are described. Statistical analysis was performed using IBM SPSS Statistics (ver. 19.0; IBM, Armonk, NY, USA).

RESULTS

A total of 151 patients underwent aspiration of hip arthroplasty; of these, 56 patients were excluded. Exclusion criteria included HHA (n=9), acute PJI (n=5), or an insufficient amount of synovial fluid for performance of the AD test (n=42). Ninety-five aspirations of THA were included. These were split into two groups: the analysis group, with sufficient data to confirm or rule out PJI, and the clinical group: patients who did not meet criteria for diagnosis of PJI, but who did not undergo surgery and therefore remain cases where PJI cannot be excluded. A flowchart is shown

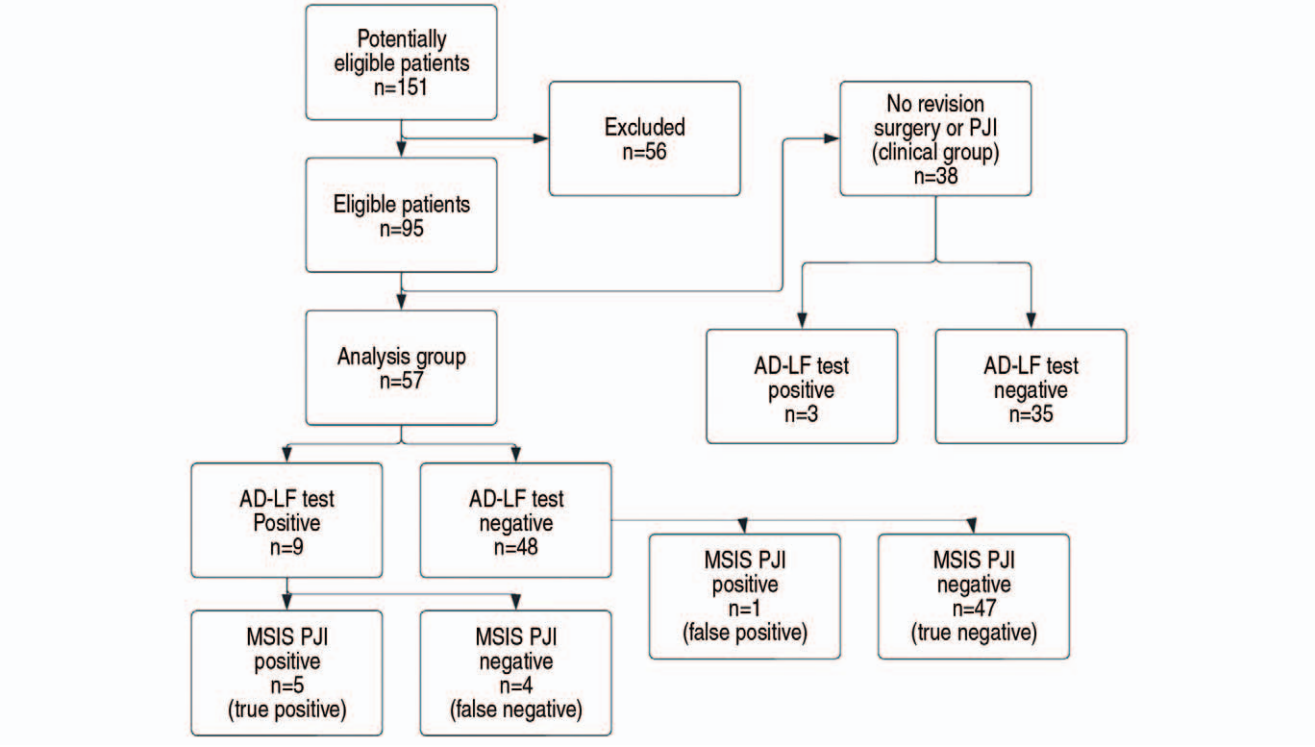

Fig. 1. Flowchart of patients, index test, and reference standard.
PJI: periprosthetic joint infection, AD-LF: alpha-defensin lateral flow, MSIS PJI: Musculoskeletal Infection Society criteria for PJI diagnosis.

Table 1. Patient, Initial Operation, and Test Characteristics

	Analysis group (n=57)	Clinical group (n=38)
Demographics		
Age (yr)	71 (38-89) (mean, 69.9)	74.5 (49-90) (mean, 71.2)
Sex		
Male	17	12
Female	40	26
ASA		
I	1	0
II	40	15
III	15	14
IV	1	1
Unknown	0	8
BMI (kg/m^2)	26.8 (21.4-34.6)	28.0 (21.4-42.0)
Deceased	0	0
Initial operation		
Time interval after THA implantation (mo)	69 (4-587)	31 (5-232)
Primary THA	35	33
Revision THA	22	5
Cemented/hybrid	21	10
Uncemented	36	28
Metal on metal	3	2
Blood tests		
CRP (mg/L)	2.7 (1-25) (n=48)	4.4 (1-171) (n=34)
ESR (mm/hr)	11.0 (2-94) (n=43)	14.5 (2-115) (n=32)
WBC count (cells/μL)	7.1 (4.1-12.4) (n=47)	7.4 (3.6-11.6) (n=33)
Aspiration results		
AD test	57	38
AD-LF test: negative	48	35
AD-LF test: positive	9	3
Aspiration cultures	52	33
Aspiration culture positive	2	0
WBC count (cells/μL)	52	31
<3,000	40	23
>3,000	12	8
PMN% >80	6	4
LE test	36	21
LE test: negative	10	1
LE test: trace	17	15
LE test: 1+	2	3
LE test: 2+	3	2
LE test: 3+	1	0
LE test: unreadable	3	0
Intraoperative tests		
Cultures	54	-
Two or more positive	1	-
One positive	9	-
Negative	44	-
Histology	27	-
Positive	3	-
Negative	24	-

Values are presented as median (range) or number only.
ASA: American Society of Anesthesiologists score, BMI: body mass index, THA: total hip arthroplasty, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: white blood cell, AD: alpha-defensin, AD-LF: alpha-defensin lateral flow, PMN%: polymorphonuclear neutrophil percentage, LE: leukocyte esterase.

in Fig. 1.

The analysis group included 57 cases of THA aspiration: 55 patients underwent hip revision surgery (seven positive AD test results), and two patients treated with suppression had definitive PJI. Both patients had a positive result for the AD test and were the only patients in the cohort with a positive culture of aspiration fluid (*Staphylococcus epidermidis* in both cases). Characteristics are shown in Table 1. None of the patients were taking antibiotics prior to, or at the time of, aspiration. Positive cultures from intraoperative samples were found in nine patients. Positive histology was observed in three cases (of 27 cases where histology was performed). Three patients had metallosis: one patient with a false positive AD-LF test result, and two patients who had a true negative AD-LF test result. The clinical group consisted of 38 patients who did not undergo surgery because of subclinical aseptic loosening with decreasing pain/wait-and-see policy (n=15) or aseptic loosening excluded/other diagnosis than PJI (n=23). All patients were excluded for analysis of AD test performance. Three patients in this clinical group had a positive result for the AD-LF test; one of these patients had metallosis. Differences in the results of aspiration and intra-operative tests between the analysis group and the clinical group are shown in Table 2.

In the analysis group, AD-LF sensitivity (MSIS criteria) was 83% (95% CI 36-100%) and specificity was 92% (95% CI 81-98%). PPV and NPV were 56% and 98%, respectively. The number of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN) and a com-

Table 2. Comparison of Aspiration and Intraoperative Results between the Analysis Group (in Which PJI Could Be Confirmed or Ruled Out) and the Clinical Group (PJI Not Confirmed nor Ruled Out but Treated according to Symptoms)

	Analysis group			Clinical group		
	Work up PJI confirmed (fistula or 3 MSIS minor criteria)	Work up PJI suspected (1-2 MSIS minor criteria	Work up PJI not suspected (0 MSIS minor criteria)	Work up PJI confirmed (fistula or 3 MSIS minor criteria)	Work up PJI suspected (1-2 MSIS minor criteria	Work up PJI not suspected (0 MSIS minor criteria)
No. of patients	2	14	41	0	16	22
Lab						
CRP>10 mg/L	1 (median, 15)	0 (median, 2)	4 (median, 2.7)		5 (median, 7)	3 (median, 3.8)
ESR>30 mm/hr	1* (94)	1 (median, 7.5)	3 (median, 11)		6 (median, 20)	1 (median, 9)
Aspiration						
AD-LF+	2	5	2 (dubious)		2	1 (MoM)
WBC count >3,000 cells/μL	1* (87,000)	11 (median, 5,500)	0 (median, 1,200)		8 (median, 3,100)	0 (median, 1,600)
PMN% >80%	1* (97%)	5 (median, 77)	0 (median, 30)		4 (median, 59)	0 (median, 28)
LE++	1*	3	0		2	0
Blood culture+	2	0	0		0	0
Intraoperative	Suppression: 2	Two-stage: 7 One-stage: 7	One-stage: 41		Suppression: 1† Extra-articular pathology: 11 No diagnosis, clinically better in time: 4	Extra-articular pathology: 13 No diagnosis, clinically better in time: 9
Cultures	-	>2 positive: 1 1 positive: 2	>2 positive: 0 1 positive: 6			
Histology+	0	3	0			
PJI+ postoperative	2 (2/2 AD pos)	4 (3/4 AD pos)	0			

PJI: periprosthetic joint infection, MSIS: Musculoskeletal Infection Society, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, AD-LF: alpha-defensin lateral flow, MoM: metal-on-metal, WBC: white blood cell, PMN%: polymorphonuclear neutrophil percentage, LE: leukocyte esterase, AD: alpha-defensin, pos: positive.

* Only performed in one case.

† Pragmatic treatment based on micro-organisms found during the DAIR (debridement, antibiotics, irrigation, and retention) procedure three years prior to inclusion.

Table 3. Diagnostic Accuracy of the Alpha-Defensin Lateral-Flow Test for Total Hip Arthroplasty

	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
MSIS									
All patients	5	4	1	47	83% (36-100)	92% (81-98)	56% (31-77)	98% (89-100)	91% (81-97)
Modified 2018 ICM									
1: All patients (inconclusive treated as infected)	9	0	8	40	53% (28-77)	100% (91-100)	100%	83% (75-89)	86% (74-94)
2: All patients (inconclusive treated as non -infected)	6	3	1	47	86% (42-100)	94% (83-99)	67% (39-86)	98% (88-100)	93% (83-98)
3: Exclusion of 'inconclusive' results	6	0	1	40	86% (42-100)	100% (91-100)	100%	98% (87-100)	98% (89-100)
EBJIS									
1: All patients (likely treated as infected)	9	0	11	37	45% (23-68)	100% (91-100)	100%	77% (69-83)	81% (68-90)
2: Exclusion of 'likely' results	9	0	10	37	47% (24-71)	100% (91-100)	100%	79% (71-85)	82% (70-91)

MSIS: Musculoskeletal Infection Society, ICM: International Consensus Meeting, EBJIS: European Bone and Joint Infection Society, TP: true positive, FP: false positive, FN: false negative, TN: true negative, CI: confidence interval, PPV: positive predictive value, NPV: negative predictive value.

parison with the other diagnostic criteria are shown in Table 3.

DISCUSSION

This prospective study that included patients with chronic painful THA was conducted in order to evaluate the results of the AD-LF test; according to our findings, sensitivity and specificity were comparable to those reported in other studies on the AD-LF test[7]. To the best of our knowledge, this is the first prospective study investigating the AD-LF test exclusively for hip arthroplasty, which is important, because PJI of the hip and PJI of the knee are probably not exactly the same[7]. For example, in this study, exclusion of one quarter of all aspirated patients was required because of an insufficient amount of fluid; in our experience, such "dry taps" are more common in hip aspirations, compared to knee aspirations. In addition, in this study the clinical group reflects the decisions and uncertainties of daily orthopedic practice: not all chronic painful THAs continue to be painful, warranting revision, especially if PJI is not confirmed in the diagnostic workup.

1. Question 1: What Is the Sensitivity, Specificity, PPV, and NPV of the AD-LF Test for Diagnosis of PJI for Chronic Painful THA?

In the analysis group, AD-LF sensitivity (MSIS criteria) was 83% (95% CI 36-100%) and specificity was 92% (95% CI 81-98%). PPV and NPV were 56% and 98%, respectively.

PJI was defined according to the modified MSIS criteria[5]. The other two criteria described obviously render different numbers for (mainly) test sensitivity, because more cases are regarded as (possibly) infected. Unfortunately, using the modified 2018 ICM criteria, many cases were considered 'inconclusive'. Although these cases were neither definitively infected nor not infected, excluding them would be a form of bias. Therefore, we chose to report the numbers considering these cases as infected, as not infected and excluding them. When using the EBJIS criteria and 2018 ICM criteria, there is another caveat: the alpha defensin test is the studied test, but also part of the definition. Thus, a positive result on the AD test enables easier fulfilment of the definition "infected". This positive feedback is a form of bias, producing fewer false positive test results.

Definitions of PJI have been revised in the last decade

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and now contain more criteria for use in diagnosis of PJI. It appears that the categories "inconclusive" (2018 ICM) or "infection likely" (EBJIS 2021) were added in order to make it less likely that absence of PJI is incorrectly stated. However, not every chronic painful THA will (or should) undergo revision. According to the current definitions of PJI, intra-operative cultures and histology are required for exclusion of a diagnosis of PJI. Because (multiple) positive intra-operative cultures result in a positive diagnosis of PJI according to each definition used, these hips can be regarded as "Schrödinger's hips". They are infected and not infected at the same time; however, we cannot be certain until we "open the box". These "Schrödinger's hips" remain an uncertain factor, leading to bias. To the best of our knowledge, most investigations of the diagnostic performances of PJI tests have been conducted with this bias. Differential verification might be a solution to this problem. Differential verification involves the use of different reference standards between patients[10]. One reference standard could be the modified MSIS PJI criteria for patients who undergo revision (so that these patients have a complete reference standard), while the other reference standard could be long-term follow-up for patients selected for a "wait-and-see" approach. With this, it would be expected that PJI patients in the cohort would eventually be identified in the long-term follow-up, therefore the follow-up is used as a proxy to obtain information regarding the true status during performance of the studied test.

2. Question 2: Which Subgroups in Which AD-LF Testing Is More (or Less) Accurate (e.g., Metallosis) Can Be Identified?

Several studies concluded that the presence of metallosis could be a misleading factor, increasing the potential for false-positive AD results[11-14]. Of the three patients with a MoM THA in the analysis group, one patient had a false positive result (MSIS not infected, 2018 ICM inconclusive due to a positive AD test result and EBJIS infected due to a positive AD test result) and two were true negative. Therefore, despite being a very small subgroup, in this study, one out of three patients with MoM had false positive results. We would advise refraining from use of the AD test in the diagnostic workup of chronic painful hip arthroplasties for MoM patients, at least until studies including larger MoM groups have been conducted.

A second possible variable is the administration of antibiotics before performing the AD-LF test. Based on the best available evidence, administration of antibiotics does not lead to a decrease of the AD level in synovial fluid[15]. Antibiotic use was not an exclusion criterion in this study; however, none of the included patients received treatment with antibiotics in the weeks prior to aspiration.

Nine patients with a HHA underwent aspiration and AD testing during the study period. A negative result was obtained for all nine patients (six patients underwent revision surgery and were definitely true negative); however, unfortunately, the sample size was too small to draw any conclusions.

A doubtful positive AD-LF test result was obtained for two patients (Fig. 2). The WBC count was 2,000-2,500 cells/μL for both patients. This study is the first in the literature to describe cases where such a doubtful positive test result was obtained. After consulting with the manufacturer, the authors decided that the results of both AD tests should be regarded as positive for PJI. A one-stage revision, including a very thorough debridement, was performed in both cases. According to the modified MSIS criteria, both cases were not infected, and were only considered infected when the 2018 ICM criteria (1/2, the other being inconclusive) and EBJIS criteria (2/2) were used because of the positive results of the AD tests. When the result of the doubtful AD-LF test was considered negative, these two border-

Fig. 2. Example of a doubtful positive alpha-defensin lateral-flow test (Synovasure; Zimmer Biomet).

line cases would be regarded as not infected and inconclusive, respectively (2018 ICM criteria), and likely but not confirmed (EBJIS, both), demonstrating the bias we anticipated in advance. If borderline test results are the only sign of infection, they should be considered with caution and should be used as a "guide value" rather than a "cut-off value". If revision is indicated in these cases, apart from the test results, a one-stage revision with thorough debridement and intraoperative cultures and histology could be considered, especially since obtaining positive cultures during revision surgery is not associated with inferior survival in the short-term (up to two years)[16]. Follow-up or repeat aspiration would be an alternative approach in cases where revision is not indicated.

The main caveat of this study is that not every patient underwent all possible tests: due to the hospital infrastructure, histology was not performed in all cases, and sonication was not possible. The LE test was not performed in some cases because of low yields. In addition, due to the patient centered design of this study, not all patients underwent revision surgery. It should be noted that selecting the revision cases does introduce bias. If, understandably, such a selection is made, the use of follow-up or repeat aspirations is advised as the second arm for differential verification of these "Schrödinger's hips", in order to ultimately determine the true accuracy of tests for diagnosis of PJI and their role in the diagnostic work up of patients with chronic painful arthroplasties.

CONCLUSION

The AD test, which is a useful addition to the arsenal of tests available for diagnosis of PJI, can be helpful to the surgeon and patient in the decision-making process. Because not all patients will undergo revision surgery, we suggest incorporating differential verification for the accuracy of PJI testing in groups of patients with painful arthroplasties. One reference standard (PJI definition) is used for verification of all patients with a positive index test result and a second reference standard (follow-up or repeat aspirations) is used for verification of all patients with a negative result.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

SUPPLEMENTARY MATERIALS

Supplementary data is available at https://hipandpelvis.or.kr/.

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