Diagnostic accuracy of the BJI InoPlex™ (Diaxonhit) immunoassay on blood samples for periprosthetic joint infection in complex microbiological situations. Preliminary results of 24 cases in a French Reference Center for Complex Bone and Joint Infection (CRIOAC)

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Original article

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Abstract

Background:

While joint aspiration is the benchmark for diagnosing periprosthetic joint infections (PJI), the results can be flawed because certain bacteria are difficult to culture, the patient is on concurrent antibiotic therapy or in some cases, repeated joint aspirations confer conflicting results. The BJI InoPlex™ (Diaxonhit) is a multiplex ELISA (Enzyme Linked Immunosorbent Assay) that measures the immune response (presence of specific IgG) to certain bacterial species from three families: *Staphylococcus (8 antigens) epidermidis, aureus* and *lugdunensis*, *Streptococcus* B (4 *antigens*) and *Cutibacterium acnes (4 antigens*). This assay is done with peripherally collected blood. However, there are few published studies about this assay, especially if the microbiological diagnosis is in doubt in cases of suspected chronic PJI. This led us to conduct a retrospective study in a French tertiary care center to determine 1) the sensitivity and specificity of the BJI InoPlex™, 2) its positive (PPV) and negative predictive value (NPV) and 3) what causes diagnostic errors.

Hypothesis:

The BJI InoPlex has a sensitivity/specificity and PPV/NPV above 75%.

Materials and Methods:

The BJI InoPlex was used 24 times on 24 patients between January 2016 and January 2017 in scenarios where the microbiological diagnosis was difficult: 1 with on-going antibiotic therapy, 13 conflicting repeat joint aspirations, 10 negative cultures with history of infection and/or clinical evidence of a PJI. The series consisted of 11 hip arthroplasty and 13 knee arthroplasty cases. The results of the BJI InoPlex test were compared to the MusculoSkeletal Infection Society (MSIS) the criteria for a joint infection.

Results:

For the bacterial species covered by the test, the sensitivity of the BJI InoPlex for diagnosing a chronic PJI based on the 2018 MSIS criteria was 50%, the specificity was 56%, the PPV was 36% and the NPV was 69%.

Discussion:

While innovative, minimally invasive, and rapid (results in a few hours), the BJI InoPlex does not provide an effective diagnosis of chronic PJI in complex microbiological situations. In this study, we used the test in the most difficult situations possible and on a small number of patients, which may explain why the results were not as good as in other studies. Its current performance and cost mean there is no role for it in our algorithm for treating patients with a suspected PJI, contrary to other biomarkers. Its spectrum must include other bacterial strains involved in chronic PJI. Knowledge of the specific infectious agent increases its diagnostic value, it could be used to monitor the outcome of a PJI, although other studies would be needed to support this use.

Level of evidence: IV – Retrospective diagnostic study

Keywords: periprosthetic joint infection, BJI InoPlex, diagnosis, joint aspiration, immunoassay, biomarkers

1. Introduction

The diagnosis of infections after joint arthroplasty is vital to the successful treatment of periprosthetic joint infections (PJI). This may be difficult [1] especially in the presence of vague symptoms [2], fragile and/or slow growing infectious agents [3,4], recent or on-going antibiotic therapy [5], or in some instances, because the diagnostic tests used provide conflicting results [6]. Preoperative diagnosis of a PJI is based on multiple examinations, of which joint aspiration for microbiological culture is the current gold standard [7]. For all that,

preoperative cultures, even repeated ones [8] can be at fault, particularly in situations described above, especially in patients who may have undergone multiple surgeries [9]. These complex scenarios have led to the development of new diagnostic techniques for PJI [10]: alpha-defensin rapid diagnostic test [11-13] (Synovasure™, Zimmer Biomet, Warsaw, IN, USA), leukocyte esterase test [14], sonication combined with molecular biology techniques [15,16], measurements of calprotectin [17]. The aim was to use these new biomarkers to improve the reliability of the tests, improve their reproducibility and improve result turn-over, compared to standard microbial culture. These tests are generally done in the context of a strong clinical suspicion of PJI, or even in the case of an acute infection requiring joint aspiration or joint incision [10-17].

The BJI InoPlex™ (Diaxonhit) is a multiplex ELISA (Enzyme Linked Immunosorbent Assay) that measures the immune response (presence of specific IgG) to certain bacterial species from three families: *Staphylococcus (8 antigens) epidermis, aureus* and *lugdunensis*, *Streptococcus agalactiae* (group B streptococcus) (4 *antigens*) and *Cutibacterium acnes (4 antigens*). This test is not very invasive since it only requires a peripheral blood test.

However, there is a paucity of published data regarding this assay other than by its designers [18], or in a case series with both early and late postoperative infections [19]. Most importantly, there is very little data in scenarios of challenging microbiological diagnoses [18-20]: conflicting results of repeated joint fluid cultures, negative cultures despite suggestive clinical and laboratory findings in patients who have a history of infection, on-going antibiotics therapy. This led us to conduct a retrospective study to determine 1) the sensitivity and specificity of the BJI InoPlex™, 2) its positive (PPV) and negative predictive value (NPV) and 3) what causes diagnostic errors. We hypothesized the BJI InoPlex had a sensitivity/ specificity and PPV/NPV greater than 75%.

2. Materials and methods

2.1 Patients

This retrospective study was done on a cohort of patients enrolled prospectively over a 1 year period who had complex microbiological situations with suspected chronic PJI (conflicting repeat joint aspiration results, negative cultures with clinical evidence of PJI, on-going antibiotic treatment) with at least 6 months' follow-up after the procedure. The study was limited to hip or knee PJI diagnoses. Among the 392 cases of PJI treated at our facility during the inclusion period, the BJI InoPlex was applied in 30 instances of ambiguous microbiological diagnosis. Use of the test was dependent on the availability of reagents supplied by Diaxonhit and the technician trained to do this test. While 30 tests were performed, 6 patients were not included because they had not undergone simultaneous culture of joint fluid. The resulted in 24 tests (Figure 1) done between January 2016 and December 2016 at a French Reference Center for Complex Bone and Joint Infection (CRIOAC) in Lille-Tourcoing in 24 patients (12 men, 12 women) who had a mean age of 63 years ± 11 [41-80] and the following characteristics:

- Hip arthroplasty (n = 11) or knee arthroplasty (n = 13) completed a mean of 3.4 ± 1.9 years [0.5-10] years prior.
- Conflicting results of repeat joint aspiration (n = 13), negative cultures with history of infection and/or clinical evidence of PJI (n = 10), on-going antibiotic therapy (n = 1).

The patients had no history of autoimmune disorders or diseases contributing to relative immunosuppression. None were undergoing immunotherapy during the study period.

2.2 Methods

A senior surgeon who was the head of the CRIOAC Nord Lille-Tourcoing underwent training specific to the InoPlex test and determined the indication for all the tests. Blood was drawn by a nurse during the surgical consultation, then sent to the laboratory to measure C-

reactive protein (CRP) and to do the serological tests. The BJI InoPlex test was performed as recommended by its manufacturer, Diaxonhit. On the same day, joint aspiration of the target joint was done in the operating suite under strict aseptic conditions and the fluid sent to the same microbiology laboratory.

The patients were informed about the use of this test but did not need to sign a specific consent form since the standard diagnostic procedures (CRP and joint aspiration) were applied. The immediate results of the test did not alter the patients' care since the results of the joint fluid culture were the benchmark.

2.3 Assessment methods

The results of the tests were compared to the 2018 criteria for PJI set out by the Musculoskeletal Infection Society (MSIS) [21] (Table 1) with validation during the multidisciplinary team (MDT) meeting of the CRIOAC Nord Lille-Tourcoing to decide whether the joint was infected or not (aseptic). The patients' care, determined during the MDT meeting, was not modified by the results of the BJI test.

2.4 Statistics

The negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity were calculated. The main endpoint – infected joint or aseptic joint – was based on the MSIS criteria related to the surgical samples collected or to the joint aspiration when no deep tissue samples were collected (11 cases not reoperated within 1 year of the sample collection).

3. Results

3.1 Patients

The patients' care pathway is summarized in Figure 1. According to the MSIS, 8/24 patients had an infected joint (33%). In the 24 patients, 18 patients (75%) had CRP less than 10 mg/L,

3 patients (12.5%) had CRP between 10 and 30 mg/L and 1 patient (3.5%) had CRP above 30 mg/L.

Two patients (8%) had cutaneous evidence of a fistula (drainage, inflammation of wound). Ten patients (40%) had local signs (pain, joint effusion, inflammation, lymphoedema). One patient had a history of PJI (methicillin-susceptible *S. aureus*) and one patient was on antibiotics (amoxicillin) for an ORL infection at the time of the test.

None of the patients were on immunosuppressants and none had signs of a chronic inflammatory disease. Lastly, none of the patients in this case series had been hospitalized during the 3 months prior to the test.

3.2 Agreement of BJI test results with culture findings

The results are summarized in Table 2. Five patients (21%) who had a positive BJI test with consistent culture results were considered as "true positives" for the targeted bacteria:

- One patient had anti-staphylococcus antibodies on the BJI with *S. pasteuri*, *S. epidermidis* and *Corynebacterium striatum* found in the culture.
- One patient had antibodies to Staphylococci and C. acnes with *S. hominis*, *C. acnes* and *Bacillus* found in the culture.
- One patient had anti-staphylococcus antibodies on the BJI with *S. aureus* identified in the joint fluid.
- One patient had antibodies to Staphylococci and Streptococcus with *S. epidermidis* and *S. agalactiae* found in the culture.
- One patient had anti-staphylococcus antibodies on the BJI with *Streptococcus sanguinis* found in the culture of a single joint aspiration.

Five patients (21%) had a negative BJI test but had positive culture results for microorganisms included in the test, thus were considered as "false negatives" for the targeted bacteria:

- Two patients had infections by multiple microbes: *S. epidermidis*, *C. acnes*, *S. saccharolyticus* in one and *S. epidermidis* and *C. acnes* in the other.
- One patient had a *C. acnes* infection.
- Two other patients had an *S. epidermidis* infection.

Six patients (25 %) had a positive BJI test with conflicting culture results, thus were considered as "false positives" for the targeted bacteria:

- Four patients had anti-staphylococcus antibodies on the BJI with positive cultures for *C. acnes* in one patient, *Gemella* spp in another patient, and no growth in two patients.
- Two patients had antibodies to *C. acnes* with one having a positive culture to *S. epidermidis* and the other having no growth.

Eight patients (33%) had a negative BJI test combined with negative cultures.

3.3 Agreement of BJI test results with PJI according to MSIS criteria

The results are summarized in Table 3 and Figure 1.

- Four patients had positive BJI results consistent with cultures and had positive PJI criteria (true positives)
- Four patients had negative BJI despite positive PJI criteria (false negatives).
- Seven patients had a positive BJI test despite being negative for the PJI criteria (false positives).
- Nine patients had a negative BJI test and negative PJI criteria (true negatives).

Thus, the sensitivity of the BJI InoPlex for diagnosing a chronic PJI based on the 2018 MSIS criteria was 50%, the specificity was 56%, the PPV was 36% and the NPV was 69%.

4. Discussion

This is the first report in France of how the BJI InoPlex performs for diagnosing chronic PJI under complex microbiological conditions. Our hypothesis was not confirmed, and led us to stop using this test for diagnosing PJIs in favor of other tests with better sensitivity or with better NPV such as the alpha-defensin test (NPV = 98%)[11] and leukocyte esterase test (NPV = 95%)[22].

Since the diagnosis of an infection is made based on a range of evidence, reliable tests are needed, especially in complex scenarios. The relevance of biomarkers is accepted universally. Shahi et al. [14] highlighted that levels of d-dimer were higher in patient with a PJI either at the hip or knee using a threshold of 850 ng/mL with a sensitivity of 89% and specificity of 93%. During a two-stage revision, patients with an obvious infection had higher d-dimer levels during the second surgical procedure. Thus d-dimer, leukocyte esterase and alpha-defensive were included in the new MSIS criteria of 2018 for a PJI [21].

Marmor et al. [18] found a sensitivity and specificity of 72% and 81% for Staphylococcus, 75% and 93% for *S. agalactiae*, 38% and 85% for *C. acnes* with a research-only version of the BJI InoPlex, which was better than in our study. This can be explained by the fact the test was used on two distinct populations: non-infected (n = 279/455) and infected (n = 176) with skin fistulae (n = 46). Our study was done with a single population of infected and non-infected patients, which likely reduced the test's performance. The aim was to test the BJI in routine clinical care on all patients suspected as having a PJI, so as to avoid recruitment bias. Also, our results were inferior to those reported by De Seynes et al. [19] who had a PPV of 97% and NPV of 72%; however, in their study, the prevalence of infection was high (63%, 45/71) and the control group was made up of patients with aseptic loosening, with the test value limited solely to Staphylococcus infections. In a multicenter study, Bémer et al. [20] had poorer results than in previous studies [18,19] when they evaluated 115 patients with a 42% prevalence of infection (49/115); the PPV was only 58%

and the NPV 91% for Staphylococcus infections. Bémer et al. [20] had to repeat the BJI in 29 of 115 patients (25%) to achieve a valid result. This protocol deviation is not insignificant, although it did not stop the authors from concluding that this serological test was not sufficient to make a PJI diagnosis for the bacteria targeted in the BJI test. Contrary to the other studies [18-20] that compared two groups made up of paired samples, in our study, the BJI test was used in routine practice in complex situations with continuous enrollment, which may largely explain our inferior results.

This test cannot be used alone, as it targets only the three main families of bacteria found in PJI, and like other biomarkers, does not provide information about their sensitivity to antibiotics. The spectrum is obviously wide enough to detect many PJIs, although it is not sufficient to explore other microorganisms often found in these same infections. Titecat et al. [23] showed that the bacteria causing PJI were mainly coagulase-negative staphylococci (38%), *S. aureus* (19%), Streptococci (8%), enterococci (5%), Gram-negative bacilli (17%), strict anaerobic bacteria (6%) such as *C. acnes* (4%), Gram-positive bacilli (3%), and about 15% polymicrobial infections (this makes up about 22% of infections, which given the current performance of the BJI test, would not be detected) [24]. In the first BJI study by Marmor et al. [18], this test could only detect 60% of all the pathogens responsible for a PJI. This test is not sufficient in routine clinical use to confirm or invalidate a PJI by itself, since its spectrum of detection is too limited and can generate false negative results. The test's performance in our study is not altered by bacteria not targeted by the BJI since the latter (*Gemella, Bacillus, Clostridium*) were found in polymicrobial cultures, associated with a positive BJI test with positive culture in three of these cases.

This test is currently an extra cost for treating PJI, thus its validity must be confirmed in the postoperative period. Marmor et al. [18] observed worse accuracy overall in the first 3 months after the procedure. This lower accuracy was also found by Saint-Vincent et al. [11]

with the alpha-defensin test within the first 2 months postoperative, like Yi et al. [25] had for serum markers (CRP, erythrocyte sedimentation rate). Thus, joint aspiration remains the gold standard both in acute and chronic situations.

Several questions can be raised about how we interpreted the test results. Some false negatives can be observed in early postoperative infections since the test is less accurate. Moreover, the patients in our study were suspected of having a chronic, non-acute PJI since the arthroplasty had been done about 3.4 years before the test, making this possibility very small. False positives also bring up the possibility of concurrent infection at other sites (endocarditis, pneumonia) or sequelae of recent infections at other sites. Since we have no information about how long the antibodies need to remain in the blood (e.g. *C. acnes* infection) to detect an infection, it would have been interesting to do a parallel study of patients with known chronic PJIs to evaluate how the antibodies change over time.

Although our study was prospective and used the MSIS criteria (the gold standard) as the outcome measure, it had certain limitations: 1) While we treated a larger number of PJI during the study period (n = 392), we chose to apply the BJI test to hip and knee arthroplasties that had an uncertain microbiological diagnosis labelled as complex, which fortunately is a fairly rare situation. 2) The number of cases was limited although it allowed us to do 24 tests during the period that the test reagents were available to us. When compared to other studies, our population was limited but it was gathered during routine care, without changing our decision algorithm. Also, our population was homogeneous in that it only included chronic infections where the microbiological diagnosis was in doubt. 3) This preliminary study could have been done on cases that were less complex microbiologically (no conflicting results between tests, acute situation); however, it appears that the standard methods (primarily joint aspiration) can easily make the diagnosis in most cases. 4) While complex microbiological cases were selected, we made sure not to include

patients receiving immunosuppressant therapy, which could have placed the test is an even more challenging situation. The conflicting results with cultures and MSIS criteria led us to stop using the test. Even though the BJI InoPlex did not alter our patient care, it has an additional cost in terms of materials and technician time to process the samples that is by no means insignificant. 5) The diagnosis of PJI is largely based on preoperative joint aspiration and on the MSIS criteria, which could have generated classification bias during the initial microbiological culture when it was negative; however, all cases were discussed in an MDT meeting to limit this bias.

5. Conclusions

While the BJI InoPlex is innovative, minimally invasive and the results are available quickly (within a few hours), it is not effective at diagnosing PJIs. Its current performance and cost indicate that there is no role for it in our algorithm for treating patients with a suspected PJI, contrary to other biomarkers. While this is an interesting concept, it would likely need to include other bacteria often found in chronic PJIs to widen its scope of application and thereby its effectiveness. Other studies could be done with new parameters, such as the monitoring of diagnosed and treated infections, before validating its use in daily clinical practice.

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Conflicts of interest: The authors have no conflict of interest to declare relative to this work. Outside this study, Henri Migaud is the editor-in-chief for Orthopaedics & Traumatology:

Surgery & Research and is a research and educational consult for Zimmer-Biomet, Corin, MSD and SERF. Outside this study, Sophie Putman is a research and educational consultant for Corin. Outside this study, Eric Senneville is a paid speaker for Zimmer and is a consultant for MSD, Pfizer, Correvio, Bayer, Sanofi-Aventis, Cepheid. The other authors have no conflict of interest to declare outside this study.

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Author contributions: JD: data collection and writing, PM: data analysis and writing, JT: data analysis and writing, FW: carried out BJI tests and cultures, SP: data analysis and writing, CL: carried out BJI tests and cultures, ES: test indication, data analysis and writing, HM: test indication, data analysis and writing.

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Table 1: 2018 criteria for periprosthetic joint infection of the MusculoSkeletal Infection Society (MSIS) [20]

Major criteria (at least one of the two major criteria)				**Decision**
Two positive cultures to the same agent in standard media				Infected if one of the two is present
Presence of a fistula communicating with the item or visible implant				
Minor criteria	Threshold		Score	**Decision**
	Acute infection	Chronic infection		
Serum CRP (mg/L) or d-Dimer (µg/L)	100 NA	10 860	2	Addition of pre- and postoperative data: ≥ 6 = infection 3 to 5 = inconclusive, continue investigations < 3 = not infected
ESR (mm/hr)	No value	30	1	
Elevated synovial fluid WBC (cells/µL) or Leukocyte esterase (urine strip) or Positive alpha-defensin (signal/cutoff)	10000 ++ 1	3000 ++ 1	3	
High synovial PMN percentage (%)	90	70	2	
Positive culture			2	
Positive histology			3	
Intra-operative purulence when ARMD is not suspected			3	

Table 2: Details results of the joint aspiration and BJI InoPlex™ test

Number of positive BJI tests with similar cultures for bacteria targeted by the test	5 (21%)
Number of positive BJI tests with conflicting cultures for bacteria targeted by the test	6 (25%)
Number of negative BJI tests with positive cultures [a]	5 (21%)
Number of negative BJI tests with negative cultures	8 (33%)

[a] Positive culture for bacteria targeted by the test

Table 3: Diagnostic performance of BJI InoPlex test and agreement between BJI and PJI by MSIS criteria

Performance of BJI InoPlex™	**Infection per MSIS**	**No infection per MSIS**
BJI +	4	7
BJI −	4	9

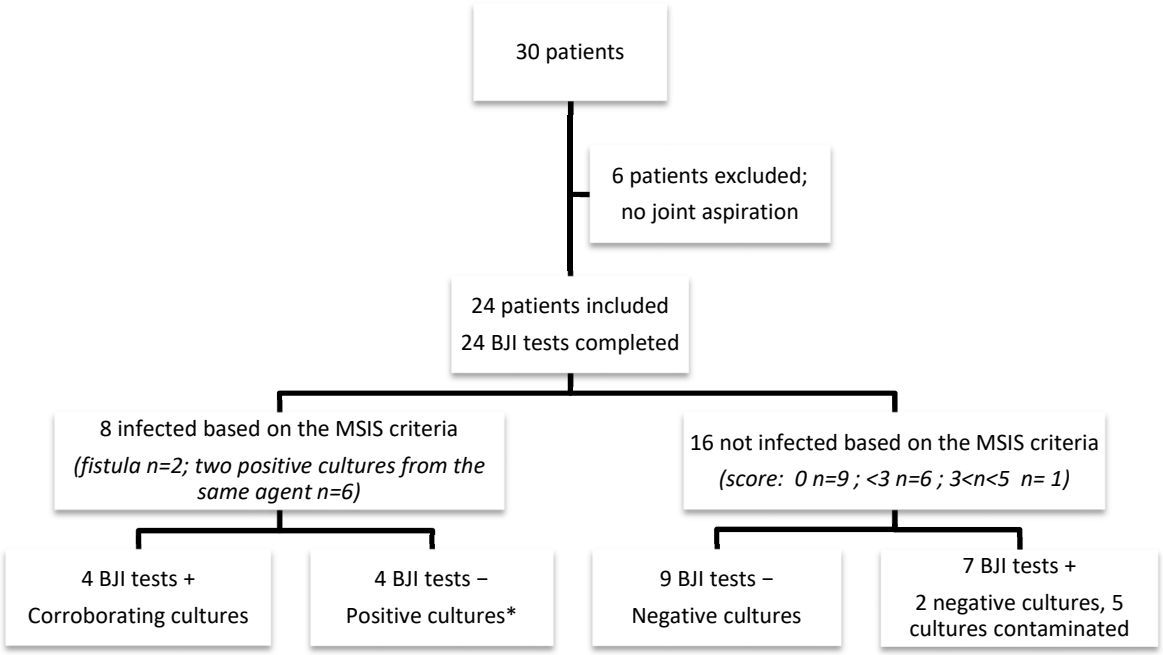
MSIS: MusculoSkeletal Infection Society [20]

sensitivity: 50%; specificity: 56%; positive predictive value: 36%; negative predictive value: 69 %

Figure legends

Figure 1: Methodology

Figure 1:



**culture positive for bacteria targeted by the test*