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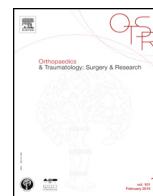
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Original article

Diagnostic accuracy of the alpha defensin lateral flow device (Synovasure) for periprosthetic infections in microbiologically complex situations: A study of 42 cases in a French referral centre

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ABSTRACT

Background: Joint aspiration is currently the reference standard test for diagnosing periprosthetic joint infection (PJI) despite the high rate of false-negative results, of which a major cause is the fastidious nature of some microorganisms. A rapid diagnostic test that detects alpha defensin (Synovasure™, Zimmer, Warsaw, IN, USA) in joint fluid can provide the diagnosis of PJI within a few minutes across the full spectrum of causative organisms (including mycobacteria and yeasts). Its performance in detecting bacterial infections is unaltered by concomitant antibiotic therapy. Few studies of Synovasure™ have been conducted by groups that were involved in designing the test, which has not been validated in France. Assessments in referral centres where complex microbiological situations are common hold considerable interest. The objective of this prospective study was to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and causes of error of Synovasure™ used to diagnose periprosthetic infection in complex microbiological situations.

Hypothesis: The rapid diagnostic test Synovasure™ has greater than 90% NPV for detecting periprosthetic infections in complex microbiological infections.

Material and methods: Synovasure™ was used 42 times in 39 patients between October 2015 and October 2017 in challenging microbiological situations [discordant joint aspiration results ($n=20$), negative cultures with clinical or laboratory evidence of infection, ($n=21$), and concomitant antibiotic therapy ($n=1$)]. Of the 39 patients, 23 had total knee prostheses, 13 total hip prostheses, and 3 total femoral prostheses. The reference standard to which the Synovasure™ results were compared was the PJI criteria set developed by the Musculoskeletal Infection Society (MSIS).

Results: Synovasure™ was negative in 30 cases with negative joint fluid cultures (30/42, 71.4%). Of the 12 (28.6%) cases with positive Synovasure™ results, only 7 (7/12, 58.3%) had positive joint fluid cultures. According to the MSIS criteria 9 cases were infected, including 8 with positive and 1 with negative Synovasure™ results. Of the 33 cases that were not infected according to MSIS criteria, 29 had negative and 3 positive Synovasure™ results; the remaining case had a positive Synovasure™ result but was excluded when metallosis was found intra-operatively. NPV was 96.7%, PPV 72.7%, sensitivity 88.9%, and specificity 90.6%.

Discussion: The high NPV of Synovasure™ suggests a role for this test in microbiologically complex situations as a new tool for ruling in and, most importantly, ruling out infection in doubtful cases.

Level of evidence: III, prospective study of diagnostic accuracy.

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1. Introduction

An accurate and rapid diagnosis is crucial to the optimal management of periprosthetic joint infection (PJI) [1] but may be difficult to achieve for reasons including the poor correlations among diagnostic criteria [2], the fastidious nature of some microorganisms that are fragile or slow to grow, the concomitant administration of antibiotics, and the at times discordant results of investigations [3]. Of the many available investigations [2,4], joint aspiration with microbiological studies is the reference standard for the preoperative diagnosis of PJI [5]. However, false-negative results are common, chiefly due to concomitant antibiotic therapy and/or to the long culture times needed to identify some microorganisms.

Alpha defensin is a protein whose concentration in joint fluid increases in the event of infection [6–8] due to any type of microorganism (including fungi and mycobacteria), even during concomitant antibiotic therapy [9–11]. The lateral flow immunoassay Synovasure™ (Zimmer, Warsaw, IN, USA) is a rapid diagnostic test that detects alpha defensin (Synovasure™) in joint fluid, thus ensuring the prompt diagnosis of PJI [12,13]. Joint metallosis, however, produces false-positive results [10]. Synovasure™ has shown good performance [12,14] in patients with strongly suspected PJI, particularly in acute situations. However, few studies have been conducted by groups that were not involved in designing the test, which has not been validated in France. Furthermore, studies are needed in referral centres for complex osteo-articular infections, where challenging microbiological diagnoses are common.

The objective of this prospective study was to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and causes of error of Synovasure™ used to diagnose periprosthetic infection in complex microbiological situations. The working hypothesis was that the rapid diagnostic test Synovasure™ had greater than 90% NPV for detecting periprosthetic infections in complex microbiological infections.

2. Material and methods

2.1. Patients

A prospective study was conducted over the 2-year period from October 2015 to October 2017 in cases raising diagnostic challenges (discordant results of repeated joint aspirations, negative cultures despite other evidence of infection, ongoing antibiotic therapy, or history of infection) seen at the referral centre for complex osteo-articular infections in Lille-Tourcoing, France. Synovasure™ was used 42 times in 39 patients, 24 males and 15 females aged 35 to 87 years. Repeated joint aspirations yielded conflicting results in 20 (47.6%) cases, and joint fluid cultures were negative despite clinical or laboratory evidence of infection in 21 (50%) cases; in 1 (2.4%) case, antibiotic therapy was ongoing in a patient with a prosthesis and multiple previous surgical procedures while deciding whether revision surgery was in order. Of the 39 patients, 14 (35.9%) had a history of infection in the same joint, 15 (38.0%) had experienced wound-healing disorders after the primary arthroplasty, and 3 (7.7%) were referred from another institution due to uncertainty about the diagnosis. Most patients had a history of multiple surgical procedures on the same joint, with a mean of 3.2 ± 2.5 (range: 1–10) and 29/39 (74.4%) patients having had at least two arthroplasties. Of the 39 patients, 23 had total joint prostheses, 13 total hip prostheses, and 3 total femoral replacements (Appendix 1). Mean time from prosthesis implantation to the Synovasure™ test was 32.1 ± 37.0 months (range: 2 = 168 months) (Appendix 1).

2.2. Methods

A senior surgeon (HM) received specific training in the use of Synovasure™ then performed or monitored the 42 tests. The test was performed on fluid recovered by routine joint aspiration for microbiological studies, which was done in the operating room under fluoroscopic guidance. A local anaesthetic was given to numb the skin and subcutaneous tissue. A few minutes later, the joint fluid was aspirated, using a new syringe and needle. The joint fluid was recovered in a blood culture bottle and seeded on standard media. Part of the fluid was processed for the Synovasure™, under non-sterile conditions. The reading kit provided the result within 10 minutes. All results were photographed and collected by the microbiology laboratory for interpretation by another reader (CL).

The patients were informed that the Synovasure™ test would be used but were not asked to sign an informed consent document, since the joint aspiration was done routinely, the test required no additional procedures, and the rapid test results had no impact on patient management, which was based on the culture results [5].

2.3. Assessment methods

The results of the 42 Synovasure™ tests were compared to the Musculoskeletal Infection Society (MSIS) criteria for PJI [15,16]. Validation was performed during a multidisciplinary meeting of the referral centre staff (Table 1).

2.4. Statistical methods

The diagnostic accuracy of Synovasure™ was assessed by computing the negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity. The reference standard for determining whether infection was present was the MSIS criteria set for PJI assessed using intra-operative samples (17/42) or aspiration fluid (25/42: 18 patients did not have surgery and 7 had a mechanical cause identified).

Table 1

Definition of periprosthetic joint infection developed by the Musculoskeletal Infection Society (MSIS) [14,15] and evaluation of these criteria in the study.

Major criteria. One major criterion indicates infection	Minor criteria. Four or more minor criteria indicate infection
Sinus tract communicating with the prosthesis	CRP elevation
The same pathogen is isolated from at least two separate deep samples from the prosthetic joint	Synovial leucocyte count > 1600/mm ³
9 cases had infection diagnosed based on presence of one major criterion	Synovial neutrophil percentage > 65%
Two positive deep samples (8)	Purulence in the affected joint
Sinus tract (1)	Microorganism identified in one deep sample from the prosthetic joint
	More than 5 neutrophils per field in 5 high power fields during histologic examination of periprosthetic tissue
	33 did not have infection
	16 met none of the minor criteria
	17 met fewer than four minor criteria
	One minor criterion (10)
	Two minor criteria (5)
	Three minor criteria (2)
	Distribution
	One + sample (12)
	CRP + elevated (5)
	Leucocytes > 1600 (4)
	Neutrophils > 65% (4)
	Purulence (1)
	> 5 neutrophils/field × 5 (0)
	No patient met four or more minor criteria

Given that NPV was our primary evaluation criterion, statistical power was computed retrospectively based on the mean SD of the NPV of Synovasure™ determined from 14 previous studies (5.96%). With the alpha risk set at 5% and the mean SD of 5.96%, power was 89%. Statistical tests were conducted using (JMP-SAS, Cary, NC, USA). Values of *p* smaller than 0.05 were considered significant.

3. Results

Fig. 1 illustrates the management of the patients. Infection was diagnosed in 9/42 (21.4%) cases. In all 30 (71.4%) cases with negative Synovasure™ results, the joint fluid cultures were negative. Of the 12 (28.6%) cases with positive Synovasure™ results, 7 (58.3%) had positive cultures of the standard joint aspirates.

Of the 9 cases infected according to MSIS criteria for PJI, 8 had positive and 1 negative Synovasure™ results. Of the 33 cases that did not meet MSIS criteria (Table 1), 29 had negative Synovasure™ results and 3 had positive Synovasure™ results; Synovasure™ was positive in an additional case, which was excluded when metallosis was discovered intra-operatively (Fig. 1).

The NPV of Synovasure™ was 96.7% and the PPV 72.7%. Sensitivity was 88.9% and specificity 90.6% (Table 2). The standard joint aspiration had 94.4% NPV, 100% PPV, 77.8% sensitivity, and 100% specificity versus the MSIS criteria set. Of the 42 Synovasure™ test results, 37 (88.1%) were concordant with the results of the standard joint aspiration cultures (Table 3).

Of the 17 cases with intra-operative samples, 10 had no microorganisms identified. Of the 7 positive cases, 3 showed more than one microorganism (Table 4).

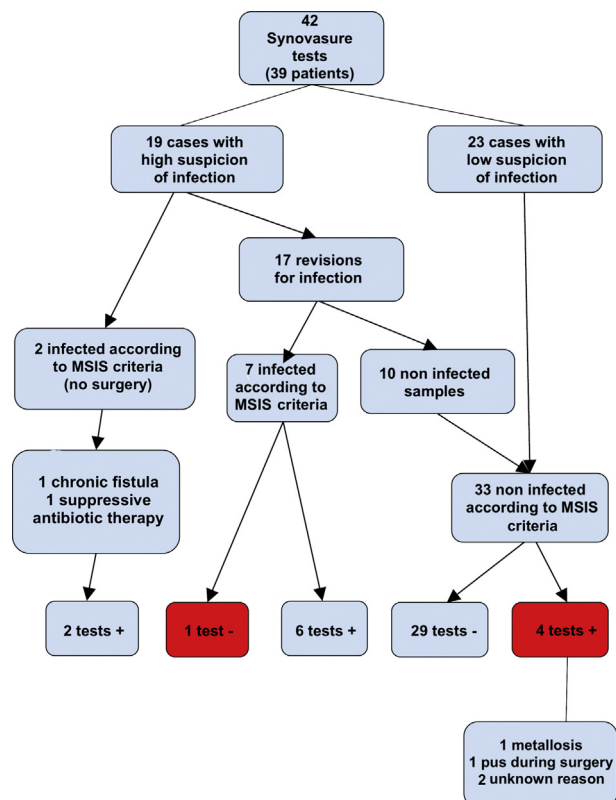


Fig. 1. Study flowchart showing the joint fluid samples and Synovasure™ results.

Table 2
Performance of the Synovasure™ test.

Performance of Synovasure™	MSIS criteria for PJI met	MSIS criteria for PJI not met
Synovasure™ positive	8	3 ^a
Synovasure™ negative	1	29

MSIS: Musculoskeletal Infection Society; PJI: periprosthetic joint infection. Negative predictive value: 96.7%; positive predictive value: 72.7%; sensitivity: 88.9%; specificity: 90.6%.

^a The patient with intra-operatively diagnosed metallosis was excluded and is not counted as a false-positive result.

Table 3
Detailed results of the joint aspirate cultures and Synovasure™.

Synovasure™ negative and cultures negative	30 (71.4%)
Number of negative Synovasure™ tests	30 (71.4%)
Synovasure™ results concordant with culture results	37 (88.1%)
Number of positive Synovasure™ tests	12 ^a (28.6%)
Synovasure™ positive and cultures positive	7 (58.3%)

^a Including one positive test in a patient with intra-operatively diagnosed metallosis.

Table 4
Results of the microbiological studies of the intra-operative samples.

Negative, n = 10	
Positive, n = 7	
Including 3 with more than one microorganism	3
<i>S. epidermidis</i>	5
<i>S. capitis</i>	2
<i>S. caprae</i>	1
<i>S. lugdunensis</i>	1
<i>Acidovorax temperans</i>	1

4. Discussion

This is the first French study of Synovasure™ used in a large population with challenging diagnostic situations managed at a referral centre for complex bone and joint infections. The results confirm the working hypothesis by showing an NPV of 96.7%. Thus, Synovasure™ may deserve a role for ruling out infection within a few minutes in complex situations. In recurrent infections, the sensitivity, specificity, NPV, and PPV of microbiological studies are decreased and novel diagnostic tools are therefore of considerable interest [17–19]. Given that the diagnosis of infection relies on a converging set of arguments, the largest possible number of tools must be available, most notably in complex cases. Synovasure™ is suitable for use in emergency situations, given the short time to results and ease of implementation and interpretation. However, Synovasure™ cannot replace cultures, which are needed to identify the microorganism and to conduct antibiotic susceptibility tests. The good performance of Synovasure™ in patients receiving antibiotics is a major advantage [10,11].

The patients were young (62 ± 13 years) for a population undergoing revision surgery and most had had multiple surgical procedures on the same joint (mean, 3.2 ± 2.5), with a long follow-up (mean, 19 months). Furthermore, 30% had a history of infection of the same joint. The cases were diagnostically challenging, with some of the patients being referred from another institution for diagnostic assistance and/or having risk factors for false-negative joint aspiration results [20,21]. In these situations, the availability of another reliable diagnostic investigation is particularly valuable.

The diagnostic performance of the alpha defensin test does not seem to be adversely affected by difficult diagnostic situations. Thus, the performance characteristics in this study were similar to the 96% sensitivity and 95% specificity of laboratory alpha defensin assays reported by Xie et al. [8]. Performance was better than in some of the earlier studies of the rapid test: Sigmund et al. [13] and Kasperek et al. [14] reported 69% and 67% sensitivity and 94% and 93% specificity, respectively. It was comparable to the results of studies by Frangiamore et al. [12] and Berger et al. [22] showing 100% and 97.1% sensitivity and 98% and 96.6% specificity, respectively.

Synovasure™ is useful for clarifying complex situations on a case-by-case basis. Its high NPV can rapidly rule out infection, thereby decreasing costs by shortening the hospital stays and diminishing the use of antibiotics. Furthermore, the lesser use of unnecessary antibiotics may have a positive impact on bacterial resistance rates. The cost of managing PJI is predicted to increase over the next few years [23]. The cost-effectiveness of Synovasure™ was not the focus of the current study but deserves to be evaluated.

This study has several limitations. First, the design was prospective, but the patients were not randomised. Cases suitable for the study are rare, making randomisation impractical. Second, the reference standard was the MSIS criteria set for PJI, which includes the results of the standard preoperative joint aspiration, leading to classification bias when the cultures are negative. However, this problem is inherent in the MSIS criteria. Third, joint fluid cytology was not performed routinely. This fact may in theory have produced two false-negative results of the MSIS criteria, but in both cases, the outcome was favourable without antibiotic therapy. Fourth, the number of cases was limited. Nevertheless, statistical power was estimated at 89% and the focus on complex cases is a strength of the study. Fifth, in 3 cases Synovasure™ could not be performed on the day of the joint aspiration, as a second opinion was required. Although this fact affected the quality of the study protocol, multiple samples were collected in the operating room in each of these 3 cases. Finally, PPV is underestimated when the prevalence of the event of interest is low in the study population. However, the primary evaluation criterion in this study was the NPV, which is the most important consideration when seeking to rule out infection in complex cases.

5. Conclusions

The use of Synovasure™ deserves consideration in patients with suspected PJI when the diagnosis is in doubt. Decisions to use Synovasure™ should be made on a case-by-case basis, given the current high cost of the test, and in combination with the conventional diagnostic investigations. Advantages of Synovasure™ include a high NPV, short time to result, and ease of interpretation even in diagnostically challenging cases.

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Author contributions

B. de Saint Vincent collected and assembled the data, H. Migaud coordinated the study and supervised the conduct of the tests, E. Senneville analysed the data and coordinated the decisions in his role as CRIOAC Lille Tourcoing referral centre coordinator, C. Loiez performed the microbiological studies, G. Pasquier and J. Girard collected the microbiological samples and performed the surgical

procedures, and S. Putman coordinated the writing of the article and the statistical analysis and management of the data.

Disclosure of interest

Henri Migaud declares interests unrelated to this study as an education and research consultant for Zimmer-Biomet, Tornier-Corin, SERF, and MSD. Gilles Pasquier declares interests unrelated to this study as an education and research consultant for Zimmer-Biomet. Julien Girard is an education and research consultant for Microport and Smith & Nephew. Eric Senneville is a paid speaker for Zimmer-Biomet and declares interests unrelated to this study as a speaker for Sanofi-Aventis, AstraZeneca, and Gilead and as a consultant for Novartis, Pfizer, and MSD. Sophie Putman is a consultant for Tornier-Corin. The other authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.otsr.2018.01.018>.

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