PROTOCOL:

Synovasure and White blood cell count after Aspiration compared to Golden standard

(January 2018)

PROTOCOL TITLE

Synovasure and **W**hite blood cell count after **A**spiration compared to **G**olden standard

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Subsidising party	
Independent expert (s)	***L.C.M. Keijser, orthopaedic surgeon***

PROTOCOL SIGNATURE SHEET

Name	**Signature**	**Date**
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INTRODUCTION AND RATIONALE

Periprosthetic joint infection (PJI) of the hip is one of the most precarious complications of total hip arthroplasty (THA). It generally requires one or more operations, weeks of hospitalization and long courses of antibiotic treatment. It is a great financial and logistic burden to hospitals and health care in general(1,2). The patients themselves, however, are the ones most afflicted by the complication. Treatment methods range from life-long suppressive antibiotic therapy (for inoperable patients with a low grade PJI) to months of living without a functioning hip articulation (Girdlestone procedure) and to curative therapy with joint replacement(2).
PJI can be hard to diagnose, and several definitions have been proposed in the past. The most current definition includes various laboratory values and aspiration results(3):

1. **two or more positive periprosthetic cultures with phenotypically identical organisms, or**
2. **a sinus tract communicating with the joint, or**
3. **having at least three of the following minor criteria:**
    a. **elevated serum C-reactive protein (CRP) >10mg/L AND erythrocyte sedimentation rate (ESR) > 30 mm/h;**
    b. **elevated synovial fluid white blood cell (WBC) count 3.000 cells/ul OR ++ result on leukocyte esterase test strip;**
    c. **elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%) >80%;**
    d. **positive histological analysis of periprosthetic tissue;**
    e. **a single positive culture**

The use of the leukocyte esterase test strip as an alternative to the synovial WBC is fairly new but has shown promising results, with positive and negative predictive values of 74% and 95% respectively(4).
Furthermore, a new diagnostic tool, the alpha-defensin (or 'Synovasure®') test has been developed recently. This point-of-care test (POCT) can show directly whether a hip arthroplasty might be infected. According to several authors, this test might be more accurate than the most commonly used tests in the abovementioned definition, with a pooled sensitivity of 0.96, and specificity of 0.97(5).
Both tests have been used in this hospital for the last year. No prior studies have been performed on these tests in the Netherlands. We aim to retrospectively include the patients that have undergone these test in our hospital, and prospectively include the patients that will undergo these test in 2018.

OBJECTIVES

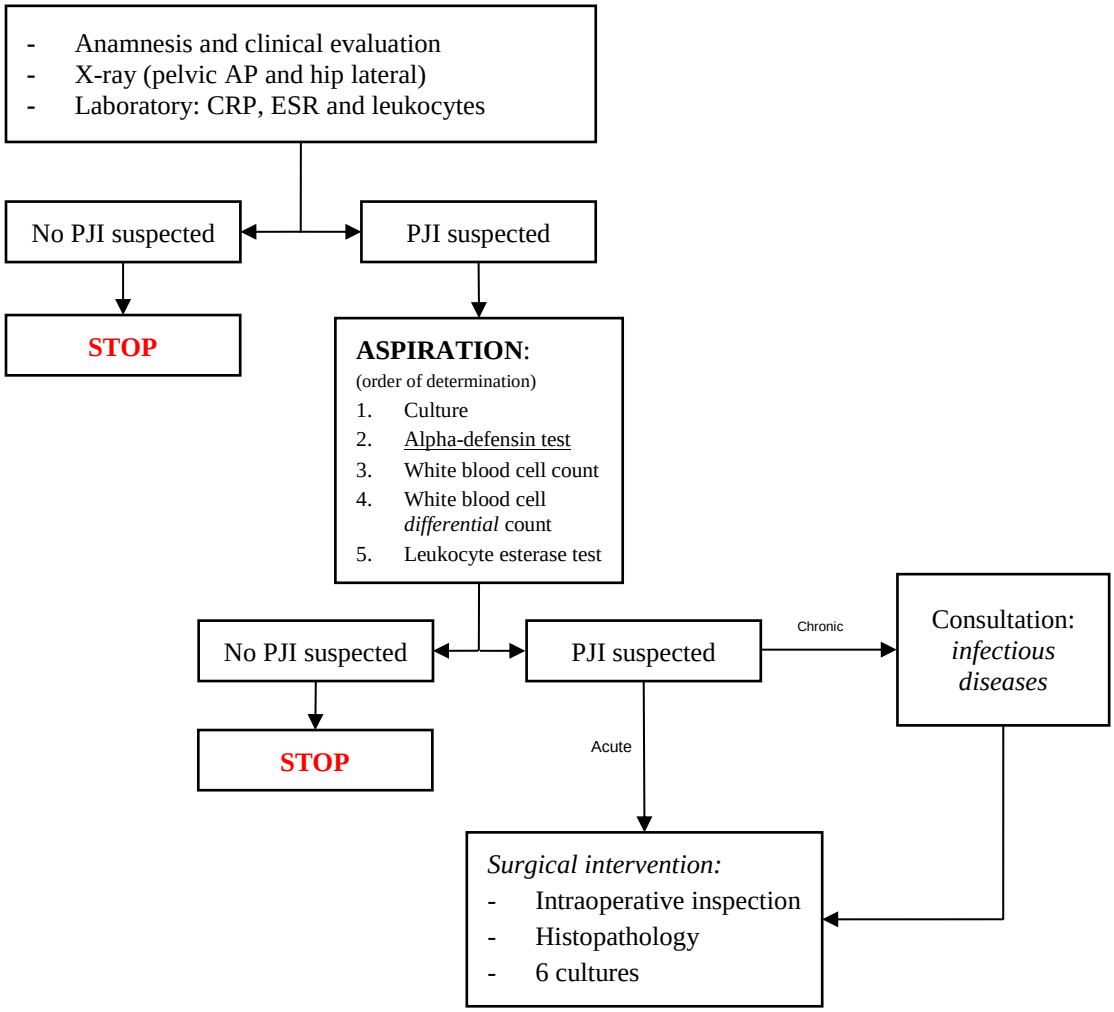
Primary Objective: What is the sensitivity and specificity of the alpha-defensin test in a Dutch population of patients with suspected hip or knee PJI?

Secondary Objective(s): What is the sensitivity and specificity of the leukocyte esterase test in a Dutch population of patients with suspected hip or knee PJI?
How does the leukocyte esterase test perform, compared to the laboratory test of synovial white blood cell count?
Which of the two tests performs better and might be of additional value in the future diagnosis of hip or knee PJI?

STUDY DESIGN

The proposed study is a single center cohort study, with patients retrospectively included for the period before January 2018 and prospectively from January 2018 forth, until the end of 2018 (December 31st) of the Northwest Clinics Alkmaar. Comparison of the synovasure alpha-defensin test and the leukocyte esterase test following joint aspiration in case of a suspected hip or knee PJI.

Figure 1: flowchart suspected hip or knee PJI



STUDY POPULATION

Population (base)

All patients that undergo aspiration of total hip arthroplasty (THA) or total knee arthroplasty (TKA) (50-100 patients per year), and all patients that underwent aspiration of total hip arthroplasty (THA).

Inclusion criteria

- Full medical record data available on PJI (e.g. all culture results)
- All possible tests performed after aspiration (alpha-defensin, leukocyte esterase, synovial white blood cell count, culture)

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Dry tap (no aspiration possible)

Sample size calculation

No power is necessary to calculate sensitivity and specificity; however, for comparison with other studies, a study population of around 100-150 would be optimal.

TREATMENT OF SUBJECTS

The intervention carried out in this study is a sterile aspiration of the hip or knee joint, which is a standard procedure as part of the diagnostic work-up in case of a suspected PJI. In this study only one test is added to the existing protocol, for which we can use the same material obtained for the other tests. No extra intervention or extended aspiration procedure is needed. Therefore, we do not consider this study as an intervention study.

Investigational product/treatment

Alfa-defensin lateral flow test (Synovasure®; Zimmer Biomet): The Synovasure Alpha Defensin Test is the first and only test specifically designed and validated for the diagnosis of Joint Infection. Developed to deliver accuracy, performance and ease of use. It was introduced to the market as a medical device in Europe and is approved by the CE (Conformité Européenne [European Conformity]).

Use of co-intervention (if applicable)

Not applicable

Escape medication (if applicable)

Not applicable

METHODS

Study parameters/endpoints

Main study parameter/endpoint

Sensitivity and specificity with the positive predictive value and negative predictive value of the Alpha Defensin Test.

Secondary study parameters/endpoints (if applicable)

- Sensitivity and specificity with the positive predictive value and negative predictive value of the leukocyte esterase test
- Laboratory tests, including C-reactive protein (CRP), leukocytes, erythrocytes sedimentation rates (ESR)
- White blood cell count
- Cultures

Randomisation, blinding and treatment allocation

Not applicable.

Study procedures

In case of a suspected hip or knee PJI, based on the anamnesis, physical examination and/or laboratory results, a joint aspiration is planned as part of the diagnostic work-up (figure 1).
The aspiration will not deviate from the standard procedure. The procedure will be performed under sterile conditions (2 times disinfections with iodine, fenestrated drape and wearing surgical gloves) at the outpatient clinic, emergency department or operating room by one of the orthopaedic surgeons or residents. In case of a hip joint aspiration it will usually be performed in the operating room with use of fluoroscopy.
If enough material is available we will divide the synovial fluid under the following tests in the following order: *culture, alpha-defensin test, white blood cell count and leukocyte esterase test.*
After all results are known we will collect them in a database.

STATISTICAL ANALYSIS

To assess the performance of the alpha-defensin test with the lateral flow device the sensitivity, specificity, positive predictive value and negative predictive value will be evaluated.

Also a 95% confidence interval will be calculated for each of the previous statistical measures.

The same analysis will be evaluated for the leukocyte esterase test.

To compare the alpha-defensin- and the leukocyte esterase test the accuracy will be calculated.

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