Prospective Study

Performance of alpha-defensin lateral flow test after synovial fluid centrifugation for diagnosis of periprosthetic knee infection

Rodrigo Calil Teles Abdo, Riccardo Gomes Gobbi, Chilan Bou Ghosson Leite, Sandra Gofinet Pasoto, Elaine Pires Leon, Ana Lucia Lei Munhoz Lima, Eloisa Bonfa, José Ricardo Pécora, Marco Kawamura Demange

ORCID number: Rodrigo Calil Teles Abdo 0000-0002-9423-6246; Riccardo Gomes Gobbi 0000-0002-1715-4343; Chilan Bou Ghosson Leite 0000-0002-8386-3121; Sandra Gofinet Pasoto 0000-0002-7343-6804; Elaine Pires Leon 0000-0001-9457-3317; Ana Lucia Lei Munhoz Lima 0000-0002-2396-9880; Eloisa Bonfa 0000-0002-0520-4681; José Ricardo Pécora 0000-0003-1621-5252; Marco Kawamura Demange 0000-0003-1999-9478.

Author contributions: Abdo RCT wrote the draft of the article, collected the samples and contributed to the data analysis, intellectual concept and design of the study; Gobbi RG reviewed the article and contributed to the intellectual concept and design of the study; Leite CBG wrote the article and contributed to the data analysis; Pasoto SG performed the laboratory tests and contributed to the strategy for alpha-defensin analysis according to its dilution; Leon EP conducted the laboratory tests; Lima ALLM contributed to data analysis, design and intellectual concept of the work; Bonfa E contributed to data analysis and intellectual concept of the work; Pécora JR and Demange MK contributed to the design and intellectual.

Supported by Fundação de

Abstract

BACKGROUND
The quantitative alpha-defensin enzyme-linked immunosorbent assay (ELISA) demands a prior synovial fluid centrifugation, whereas this processing is not routinely required prior to the alpha-defensin lateral flow test.

AIM
To evaluate whether a prior synovial fluid centrifugation could lead the lateral flow performance to achieve comparable results to ELISA during periprosthetic joint infection (PJI) diagnosis.

METHODS
Fifty-three cases were included in this study: 22 classified as PJI and 31 classified as aseptic cases, according to Musculoskeletal Infection Society 2013 criteria. Synovial fluid samples were submitted to centrifugation, and the supernatant was evaluated by ELISA and lateral flow tests. The sensitivity (SE), specificity (SP) and accuracy of each method were calculated as well as the agreement between those two methods.

RESULTS
In all of the 31 samples from aseptic patients, alpha-defensin ELISA and lateral flow tests showed negative results for infection. Regarding the 22 infected patients, the lateral flow test was positive in 19 cases (86.4%) and the ELISA was positive in 21 (95.5%). Sensibility, SP and accuracy were, respectively, 86.4%
INTRODUCTION

Total knee arthroplasty (TKA) is one of the most successful orthopedic procedures, providing excellent improvement in knee pain, function and quality of life[1]. With the population ageing and the growth incidence of symptomatic osteoarthritis, an increased number of TKA has been observed over the years[2,3]. Despite the most satisfactory results, several complications can occur after TKA, such as long-term pain, periprosthetic fractures, and joint infection[4]. Periprosthetic joint infection (PJI) after TKA is a catastrophic postoperative complication, that ranges from 0.5% to 3% of cases[5-7]. PJI can lead to serious consequences, including death[8], and accounts for a quarter of TKA revision surgeries[6], leading to a substantial economic impact on the healthcare system[9].

Although timing and precision of PJI diagnosis is critical for the patient’s evolution, there is no one-hundred percent exam to provide its confirmation. For that reason, the Musculoskeletal Infection Society (MSIS) has developed a score for unifying PJI definition[10,11]. Considering the most updated criteria, alpha-defensin has been included as a new biomarker during the investigation of PJI[10].

Alpha-defensin is a neutrophil-released antimicrobial peptide[12] that increases in response to pathogens[13]. Nowadays, both the synovial alpha-defensin tests available [the quantitative enzyme-linked immunosorbent assay (ELISA) and the qualitative lateral flow test] provide important information during the investigation of PJI[14]. However, given the higher performance of ELISA, this test has a slight advantage[15,16]. The lateral flow test, despite the inferior performance, offers benefits regarding the ease of use, time-efficiency and cost[14]. One potential reason that could reduce the measurement of the lateral flow test is regarding the differences between fluid processing. While the synovial fluid sample has to be centrifuged preceding ELISA measurement, the same processing is not routinely performed before the lateral flow,
according to the manufacturer’s instructions. Thus, the maintenance of cellular debris and other particles within the synovial fluid could interfere in the results.

Here, we aimed to evaluate the performance of the alpha-defensin lateral flow test post synovial fluid centrifugation, and compare these results with the synovial alpha-defensin ELISA. Our hypothesis was that a prior centrifugation of the synovial fluid would achieve high sensitivity and specificity to predict knee PJI, leading to equivalent performance as alpha-defensin ELISA.

**MATERIALS AND METHODS**

The study was approved by the local Institutional Review Board (2179456). Written informed consent was obtained from each patient prior to participation.

We conducted a prospective, cross-sectional diagnostic study to assess the performance of the alpha defensin lateral flow measured after synovial fluid centrifugation in patients under investigation of chronic knee PJI. Inclusion and exclusion criteria are displayed in [Table 1](#).

The primary outcome was to evaluate the sensitivity, specificity and accuracy of the lateral flow test post fluid centrifugation. Secondarily, we assessed the performance of the alpha-defensin ELISA in the same population of study, and compared the results between both modalities.

Initially, 59 patients were selected. Of these, three patients had insufficient joint fluid aspirate for analysis, and three patients were using antibiotics, being excluded from the study. A total of 53 patients were included. Figure 1 represents the flowchart of enrolled patients. The recruitment was performed between August 2016 and July 2019.

Among those 53 patients, 22 were diagnosed as infected, and 31 as aseptic. The revised MSIS 2013 criteria were used for the diagnosis of knee PJI[11].

**Intervention**

Demographic data was recorded. Clinical examination and laboratory evaluations, including serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were collected on the same day as joint aspiration. Knee aspiration was conducted using the superolateral approach, with a 21-gauge needle and a 20-mL syringe. The possible maximum volume of synovial liquid was collected. In this study, at least 3 mL of joint fluid was required for proper analysis. All aspiration procedures were performed by the same author (RCTA).

After that, the synovial fluid samples were referred to the laboratory within 2 h. Part of the fluid from each sample was sent to analysis for cell count, percentage of polymorphonuclear leukocytes and cultures from aerobic, anaerobic and fungi. The remaining fluid was centrifuged for 10 minutes at 2700 rpm to separate all cell debris and particles. The supernatant was collected and divided into 2 aliquots, as following: approximately 1 mL of synovial fluid was referred to the qualitative alpha-defensin lateral flow test; the rest of the fluid was stored at -80° C until further immunoassay analyses. To quantify synovial alpha-defensin using ELISA, approximately 1.5 to 2 mL of synovial fluid was needed.

**Qualitative alpha-defensin analysis**

For the qualitative measurement, a lateral flow test (Synovasure® Zimmer-Biomet, Warsaw, IN, United States) was used according to the manufacturer’s label. The centrifuged synovial fluid sample was diluted in the dilution buffer supplied by the kit, and deposited on the Synovasure® device. The qualitative result was read after 10 min. The result was considered positive for PJI if two lines appeared in the reading panel, regardless of its intensity.

**Quantitative alpha-defensins analysis**

For the quantitative alpha-defensin test, the commercial alpha-defensin (HNP1-3) ELISA kit (Hycult Biotech®, Uden, Netherlands) was employed. This ELISA kit is used to determine human HNP1-3. All assays were optimized and performed in duplicate by an experienced laboratory technician. The dilution optimization of the synovial fluid at 1:5000 was performed to decrease the effects of the fluid viscosity on the assay. Results were generated in optical density units (OD) using a spectrophotometer. The results in OD were plotted on the vertical axis with the corresponding concentration values on the horizontal axis (logarithmic scale). The concentration and the dilution factor were multiplied to reach alpha-defensin values in mg/L. The assay was...
Table 1 Inclusion and exclusion criteria of the study

| Inclusion criteria                                                                 | Exclusion criteria                                                                 |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Any of the following suspicious signs or symptoms of chronic knee PJI (more than 90 d), as following: | Acute signs or symptoms of knee infection (less than 90 d)                        |
| Persistent knee pain (more than 3 mo), without other apparent cause               |                                                                                   |
| Persistent joint effusion (more than 3 mo)                                        |                                                                                   |
| Persistent local heat (more than 3 mo)                                             |                                                                                   |
| Presence of draining sinus                                                         |                                                                                   |
| Early failure of the prosthesis (less than 5 yr)                                   |                                                                                   |
| Radiographic findings suggesting infection[33]                                     |                                                                                   |
| Have not used antibiotics for at least 4 wk before the evaluation                 | Insufficient synovial fluid volume during knee aspiration                         |
|                                                                                   | Insufficient data for fulfilling the periprosthetic infection criteria[11]         |

PJI: Periprosthetic joint infection.

Figure 1 Flowchart of the patients included in the study.

optimized to operate at a cutoff value of 5.2 mg/L, based on previous studies[17,18].

Statistical analysis
Shapiro-Wilk test was applied to assess normality. Continuous variables were expressed as descriptive analysis, and categorical variables were expressed as proportions. To compare continuous variables, unpaired t-test or Mann-Whitney test were used, as appropriate. Fisher's exact test was applied to compare categorical variables. The cutoff value was obtained using the Receiver Operator Curve (ROC) through the SPSS software® (version 25.0 for Mac; SPSS, Chicago, IL), giving the results as a semiquantitative signal-to-cutoff ratio (S/CO) of 1.0. Sensitivity, specificity and accuracy (and 95%CI) of each method were calculated using the MSIS 2013 criteria as standard. The agreement between ELISA and lateral flow test was evaluated based on the percentage of concordant results, and McNemar's test was performed to calculate the statistical difference between those two alpha-defensin tests. Statistical significance was set at \( P < 0.05 \).
To further investigate whether draining sinus has influenced the tests results, we also calculated sensitivity, specificity and accuracy of each method excluding patients with fistulization.

## RESULTS

Of the 53 patients included in the study, 31 were considered without infection (aseptic cases) and 22 were classified as infected. Table 2 shows the patient demographics.

In relation to the aseptic cases, all lateral flow tests showed negative results for infection. Likewise, alpha-defensin ELISA showed a mean S/CO of 0.28 ± 0.13, which was considered negative for all cases.

Regarding the infected patients, lateral flow showed positive results in 19 cases (86.4%). The 3 false negatives occurred in patients with sinus tract. The ELISA presented 21 positive (95.5%) (mean S/CO-4.93 ± 2.28) and one negative result (S/CO-0.24). Similarly, this false negative case referred to a patient with draining sinus.

Lateral flow test showed a sensitivity of 86.4% (95%CI: 65.1%-97.1%), a specificity of 100% (95%CI: 88.8%-100%) and an accuracy of 93.2% (95%CI: 82.8%-98.3%). Alpha-defensin ELISA presented a sensitivity of 95.5% (95%CI: 77.2%-99.9%), a specificity of 100% (95%CI: 88.8%-100%) and an accuracy of 98.1% (95%CI: 89.9%-100%). Table 3 summarizes those findings.

In terms of ROC analysis, area under curve was 93.2% (95%CI: 84.6%-100%) for the lateral flow test and 97.9% (95%CI: 93.6%-100%) for ELISA. The agreement between lateral flow and ELISA was observed in 51 cases (96.2%; 95%CI: 87.0%-99.5%). The two disagreement cases were false negatives for the lateral flow. No statistical difference between those two tests were found (P = 0.48).

Given that all false positive results occurred in patients with sinus tract, we performed an exploratory analysis to evaluate whether the lateral flow and the ELISA would change after excluding those selected patients (4 patients with sinus tract). In this situation, a sensitivity of 100% (95%CI: 81.5%-100%), specificity of 100% (95%CI: 88.8%-100%), accuracy of 100% (95%CI: 92.8%-100%) and agreement of 100% (95%CI: 92.9%-100%) were found for both tests (Table 4).

## DISCUSSION

The findings of this study reinforce our hypothesis that a prior synovial fluid centrifugation before the lateral flow measurement provides high sensitivity, specificity and accuracy, leading to comparable performance of the alpha-defensin ELISA, so far the best method to measure synovial alpha-defensin[15]. This preliminary finding may bring a novel concept to the major topic of PJI.

Diagnosis of PJI is frequently defiant, particularly in chronic infections in which the clinical symptoms might be subtle and inflammatory markers might be normal[19]. In this regard, a great need for new diagnostic tests is observed[20]. Alpha-defensin is a small antimicrobial peptide that acts as part of the host's innate immune response against pathogens[12]. After the pathogen insult, the release of alpha-defensin increases, and a rapid interaction of this peptide with the pathogen’s membrane occurs. As a consequence, the membrane depolarizes, and the pathogen is killed[21].

Under a knee infection, the concentration of alpha-defensin elevates into the joint. Indeed, this synovial fluid biomarker has been studied for PJI diagnosis, providing exciting findings in terms of sensitivity and specificity[14,22]. It has been demonstrated that, even in the presence of inflammatory disease or antibiotic use, the results are similar[17]. Here, we opted to exclude patients using antibiotics to avoid potential bias. However, we did include patients with inflammatory diseases, which in fact did not influence those tests' performance. Due to its relevance and applicability, alpha-defensin has been included as a diagnostic criterion in the updated consensus of PJI[10].

Currently, there are two commercially available methods for the determination of synovial alpha-defensin. The quantitative laboratory-based ELISA, that requires a centrifuged synovial fluid to assess the concentration of alpha-defensin[17], and the qualitative lateral flow test. As mentioned, both tests have shown to be successful for the investigation of PJI, with ELISA presenting the best performance[17,18,23,24]. However, alpha-defensin ELISA is much more complex, requiring a laboratory structure and an experienced professional to be performed. Conversely, the lateral flow test can be done by the physician at any location, and the result is rapidly
Table 2 Patient demographics

|                  | Total  | Aseptic cases | Infected cases | P value |
|------------------|--------|---------------|----------------|---------|
| n                | 53     | 31            | 22             |         |
| Sex              |        |               |                | 0.22    |
| Male             | 14 (26.4) | 6 (19.4) | 8 (36.4) |         |
| Female           | 39 (73.6) | 25 (80.6) | 14 (63.6) |         |
| Age (range)      | 68 (47-85) | 67 (47-85) | 70 (52-85) | 0.30    |
| Laterality       |        |               |                | > 0.99  |
| Right knee       | 28 (52.8) | 16 (51.6) | 12 (54.5) |         |
| Left knee        | 25 (47.2) | 15 (48.4) | 10 (45.5) |         |
| Inflammatory disease | 12 (22.6) | 7 (22.6) | 5 (22.7) | > 0.99  |
| RA               | 10 (18.9) | 7 (22.6) | 3 (13.6) |         |
| Gout             | 2 (3.8) | 0 | 2 (9.1) |         |
| Sinus tract      | 4 (7.5) | 0 | 4 (18.2) |         |
| Alpha-defensin S/CO | 2.21 ± 2.73 | 0.28 ± 0.13 | 4.93 ± 2.28 | < 0.01  |

1Fisher’s exact test.  
2Unpaired t test.  
3Mann-Whitney test. Values expressed in number (percentage). Age in years is presented as mean (range) and alpha-defensin S/CO in mean (standard deviation). RA: Rheumatoid arthritis.

Table 3 Statistical results of enzyme-linked immunosorbent assay and lateral flow test for all patients

|                  | Aseptic | Infected | Sensitivity (95%CI) | Specificity (95%CI) | Accuracy (95%CI) |
|------------------|---------|----------|---------------------|---------------------|------------------|
| ELISA            |         |          |                     |                     |                  |
| Negative         | 31      | 1        | 95.5% (77.2%-99.9%) | 100% (88.8%-100%)  | 98.1% (89.9%-100%)|
| Positive         | 0       | 21       |                     |                     |                  |
| Lateral flow     |         |          | 86.4% (65.1%-97.1%) | 100% (88.8%-100%)  | 93.2% (82.8%-98.3%)|
| Negative         | 31      | 3        |                     |                     |                  |
| Positive         | 0       | 19       |                     |                     |                  |

ELISA: Enzyme-linked immunosorbent assay.

expressed within 10 minutes.

As suggested by our team, one potential reason for the inferior results regarding the lateral flow test is that, during its execution, fluid centrifugation is not performed (in accordance with the manufacturer’s instruction). Consequently, some particles and cellular debris could lead to false results. Although some evidence shows that blood contamination does not influence the lateral flow reading[19], the sample processing is not equivalent between ELISA and lateral flow test, which may interfere in the device reading[15,16]. In this study, we indirectly suggest this plausible issue, since a favorable performance of the lateral flow test was reached after centrifugation. Here, we obtained a sensitivity of 86.4%, a specificity of 100% and an accuracy of 93.2%, superior values than the ones observed in some previous non-centrifuged studies. Indeed, sensitivity of approximately 67%-69%, specificity of 93%-94%, and accuracy of 85% were previously reported for the lateral flow test[25,26]. It is noteworthy to mention that, although some recent systematic reviews and meta-analyses present higher pooled values for the lateral flow, the moderate-to-high heterogeneity among the included studies compels careful interpretation. Even so, the 83% sensitivity and 94% specificity found in these studies are still slightly lower than the achieved here[14,27]. In our series, the centrifuged lateral flow performed similarly to ELISA, which also demonstrated excellent results in concordance to the literature[16,27].
Some authors have described false positive results using the lateral flow test in cases of metallosis\[23,25\] and crystal deposition disease\[28,29\]. This current study did not find any false positive case, despite the presence of four patients with gout. Once again, the centrifugation might improve the measurement by removing these particles. On the other hand, one false negative (by ELISA) and three false negatives (by the lateral flow test) were observed. All of those occurred in patients with sinus tract, as previously shown\[30,31\]. Although it was not directly investigated here, we speculate that the fistulization tends to drain the synovial fluid, avoiding the accumulation of pathogen and alpha-defensin within the knee. Considering the presence of draining sinus as a confirmation of PJI diagnosis, additional investigation would not be required. In this regard, excluding these specific patients, a sensitivity, specificity, accuracy and agreement of 100% were obtained for both tests.

The study has several limitations. First, we did not perform a direct comparison between centrifuged and non-centrifuged samples for the lateral flow test. Due to the high cost of lateral flow test in our region when this preliminary study was designed, we decided to compare these initial findings with the literature. As we know, there are several studies presenting remarkable data\[14,25,26,32\]. Further comparative trials are necessary and might add stronger conclusions. In addition, understanding the reason for false positive cases in patients with crystal arthropathy or metallosis, and the beneficial effects of synovial fluid centrifugation in these contexts may be valuable for its proper management. Moreover, despite the prospective design, the study was not randomized. Given the rarity of the cases that fit in our study, a randomization is impracticable. Therefore, we provide interesting data showing that a prior centrifugation may improve the lateral flow test performance. Considering the ease of execution and interpretation of the lateral flow, the addition of this prior step deserves further investigation and, potentially, a place in the PJI diagnosis.

CONCLUSION

In conclusion, we have identified that an extra step of synovial fluid centrifugation prior to the alpha-defensin lateral flow test achieved high sensitivity, specificity and accuracy. The results obtained using this methodology were comparable to those obtained with the alpha-defensin ELISA. Furthermore, centrifuged lateral flow demonstrated performance values slightly higher than the previously reported in the literature. Therefore, the use of the alpha-defensin lateral flow post synovial fluid centrifugation may represent a novel and interesting strategy during the PJI investigation given its lower complexity and equivalent performance in comparison to ELISA.

ARTICLE HIGHLIGHTS

Research background

Periprosthetic joint infection (PJI) is a serious postoperative complication that leads to severe morbidity as well as substantial financial burden to the healthcare system. Currently, two synovial alpha-defensin tests [the quantitative enzyme-linked
Abdo RCT et al. Alpha-defensin lateral flow with prior centrifugation

immunosorbet assay (ELISA) and the qualitative lateral flow test] are available and provide important information during PJI investigation, with the ELISA presenting slightly superior performance. However, the lateral flow test offers benefits in terms of the ease of use, time-efficiency and cost.

**Research motivation**
While the synovial fluid sample has to be centrifuged preceding ELISA, prior centrifugation is not routinely performed to the lateral flow test. The maintenance of synovial fluid debris could potentially interfere in the lateral flow results.

**Research objectives**
This study aimed to evaluate the performance of the alpha-defensin lateral flow test with prior synovial fluid centrifugation and compare the results with the synovial alpha-defensin ELISA.

**Research methods**
In this prospective study, 53 cases of total knee arthroplasty were evaluated: 22 classified as PJI and 31 classified as aseptic knees. Synovial fluid samples were collected and submitted to centrifugation, and the supernatant was evaluated by lateral flow test and ELISA. Sensitivity, specificity, and accuracy of each method as well as the agreement between those two methods were calculated.

**Research results**
Alpha-defensin ELISA and lateral flow tests showed negative results for infection in all 31 aseptic patient samples. In regard to the 22 infected cases, the lateral flow test showed positive results in 19 cases (86.4%) whereas the ELISA was positive in 21 cases (95.5%). Sensibility, specificity, and accuracy were 86.4% (95%CI: 65.1%-97.1%), 100% (95%CI: 88.8%-100%) and 93.2% (95%CI: 82.8%-98.3%), respectively, for the lateral flow test and 95.5% (95%CI: 77.2%-99.9%), 100% (95%CI: 88.8%-100%) and 98.1% (95%CI: 89.9%-100%) for ELISA. Agreement of 96.2% between these two methods were found, without statistical difference between them ($P = 0.48$).

**Research conclusions**
Alpha-defensin lateral flow test with prior synovial fluid centrifugation showed high sensitivity, specificity, and accuracy, achieving comparable results to ELISA. Given the lower complexity of the lateral flow test, a prior centrifugation might be a valuable strategy to enhance its performance.

**Research perspectives**
Prior synovial fluid centrifugation may be a novel and interesting strategy to improve the lateral flow performance during the PJI diagnosis. Further investigation is required to clarify its actual benefit.

**REFERENCES**

1. Steinhaus ME, Christ AB, Cross MB. Total Knee Arthroplasty for Knee Osteoarthritis: Support for a Foregone Conclusion? *HSS J* 2017; 13: 207-210 [PMID: 28690473 DOI: 10.1007/s11420-017-9558-4]
2. Sloan M, Premkumar A, Sheth NP. Projected Volume of Primary Total Joint Arthroplasty in the U.S., 2014 to 2030. *J Bone Joint Surg Am* 2018; 100: 1455-1460 [PMID: 30180053 DOI: 10.2106/JBJS.17.01617]
3. Price AJ, Alvand A, Troelsen A, Katz JN, Hooper G, Gray A, Carr A, Beard D. Knee replacement. *Lancet* 2018; 392: 1672-1682 [PMID: 30496082 DOI: 10.1016/S0140-6736(18)32344-4]
4. Lu J, Han J, Zhang C, Yang Y, Yao Z. Infection after total knee arthroplasty and its gold standard surgical treatment: Spacers used in two-stage revision arthroplasty. *Intractable Rare Dis Res* 2017; 6: 256-261 [PMID: 29259853 DOI: 10.5582/irdr.2017.01049]
5. Martínez-Pastor JC, Maculé-Beneyto F, Suso-Vergara S. Acute infection in total knee arthroplasty: diagnosis and treatment. *Open Orthop J* 2013; 7: 197-204 [PMID: 23919094 DOI: 10.2174/1874325001307010197]
6. Mallon CM, Gooberman-Hill R, Moore AJ. Infection after knee replacement: a qualitative study of impact of periprosthetic knee infection. *BMC Musculoskeleton Disord* 2018; 19: 352 [PMID: 30285692 DOI: 10.1186/s12891-018-2284-7]
7. Parvizi J, Ghanem E, Sharkey P, Aggarwal A, Burnett RS, Barrack RL. Diagnosis of infected total knee: findings of a multicenter database. *Clin Orthop Relat Res* 2008; 466: 2628-2633 [PMID: 18823947]
result in false-positive AS, Zingg PO, Achermann Y. Inflammatory disorders mimicking periprosthetic joint infection may
Plate A
Better Than the Alpha Defensin Lateral Flow Test for PJI Diagnosis?
Kuiper JWP
Sigmund IK
Arthroplasty
Diagnosis of Periprosthetic Joint Infection Using a Novel Alpha-Defensin Lateral Flow Assay.
Kasparek MF
Bingham J
defensin Immunoassay Test for Diagnosing Periprosthetic Joint Infection?
Bonanzinga T
[PMID: 456-460 [PMID: 27044108 DOI: 10.1073/pnas.1601831113]]
Balato G, de Matteo V, Asciome T, Di Donato SL, De Franco C, Smeraglia F, Baldini A, Maricorda M. Laboratory-based vs qualitative assessment of α-defensin in periprosthetic joint and knee infections: a systematic review and meta-analysis. Arch Orthop Trauma Surg 2020; 140: 293-301 [PMID: 31300864 DOI: 10.1007/s00402-019-03232-5]
Suen K, Keeka M, Ailabouni R, Tran P. Synovasure ‘quick test’ is not as accurate as the laboratory-based α-defensin immunoassay: a systematic review and meta-analysis. Bone Joint J 2018; 100-B: 66-72 [PMID: 29305453 DOI: 10.1302/0301-620X.100B1.BJJ-2017-0630.R1]
Ahmad SS, Hirschmann MT, Becker R, Shaker A, Atscherang A, Keel MJ, Albers CE, Buektiker L, Maquengo S, Stöckle U, Kohl S. A meta-analysis of synovial biomarkers in periprosthetic joint infection: Synovasure™ is less effective than the ELISA-based alpha-defensin test. Knee J 2018; 187 (6): 1333-1344 [PMID: 29551303 DOI: 10.1016/j.arth.2018.02.078]
Parvizi J, Gehrke T. International Consensus Group on Periprosthetic Joint Infection. Definition of periprosthetic joint infection. J Arthroplasty 2014; 29: 1331 [PMID: 24768547 DOI: 10.1016/j.arth.2014.03.009]
Ganz T, Selsted ME, Szklarek D, Harwig SS, Daher K, Bainton DF, Lehrer RI. Defensins. Natural peptide antibiotics of human neutrophils. J Clin Invest 1985; 76: 1427-1435 [PMID: 2997278 DOI: 10.1172/JCI112120]
Brook M, Tomlinson GH, Miles K, Smith RW, Rossi AG, Hiemstra PS, van’t Wout EF, Dean JL, Gray NK, Lu W, Gray M. Neutrophil-derived alpha defensins control inflammation by inhibiting macrophage mRNA translation. Proc Natl Acad Sci U S A 2016; 113: 4350-4355 [PMID: 27044108 DOI: 10.1073/pnas.1601831113]
Gray NK, Lu W, Gray M. Neutrophil-derived alpha defensins control inflammation by inhibiting macrophage mRNA translation. Proc Natl Acad Sci U S A 2016; 113: 4350-4355 [PMID: 27044108 DOI: 10.1073/pnas.1601831113]
Deirmengian C, Kardos K, Kilartin P, Cameron A, Schiller K, Parvizi J. Combined measurement of synovial fluid α-Defensin and C-reactive protein levels: highly accurate for diagnosing periprosthetic joint infection. J Bone Joint Surg Am 2014; 96: 1439-1445 [PMID: 25187582 DOI: 10.2106/JBJS.M.01316]
Deirmengian C, Kardos K, Kilartin P, Cameron A, Schiller K, Booth RE Jr, Parvizi J. The alpha-defensin test for periprosthetic joint infection outperforms the leukocyte esterase test strip. Clin Orthop Relat Res 2015; 473: 198-203 [PMID: 24942960 DOI: 10.1007/s11999-014-3722-7]
Renz N, Yermak K, Perka C, Trampuz A. Alpha Defensin Lateral Flow Test for Diagnosis of Periprosthetic Joint Infection: Not a Screening but a Confirmatory Test. J Bone Joint Surg Am 2018; 100: 742-750 [PMID: 29715222 DOI: 10.1007/JBJS.17.01005]
Corvec S, Portillo ME, Pasticci BM, Borens O, Trampuz A. Epidemiology and new developments in the diagnosis of prosthetic joint infection. Int J Artif Organs 2012; 35: 923-934 [PMID: 23138706 DOI: 10.5301/ijao.5000168]
Frangiamore SJ, Gajewski ND, Salesh A, Farias-Kovace M, Barsoun WK, Higuer CA. α-Defensin Accuracy to Diagnose Periprosthetic Joint Infection-Best Available Test? J Arthroplasty 2016; 31: 456-460 [PMID: 26545577 DOI: 10.1016/j.arth.2015.09.035]
Deirmengian C, Kardos K, Kilartin P, Cameron A, Schiller K, Parvizi J. Diagnosing periprosthetic joint infection: has the era of the biomarker arrived? Clin Orthop Relat Res 2014; 472: 3254-3262 [PMID: 24590839 DOI: 10.1007/s11999-014-3543-8]
Bonanzinga T, Zahar A, Dütsch M, Laussmann C, Kendoff D, Gehrke T. How Reliable Is the Alpha-Defensin Immunoassay Test for Diagnosing Periprosthetic Joint Infection? Clin Orthop Relat Res 2017; 475: 408-415 [PMID: 27343056 DOI: 10.1007/s11999-016-4906-0]
Bingham J, Clarke H, Spanghel M, Schwartz A, Beauchamp C, Goldberg B. The alpha defensin-1 biomarker assay can be used to evaluate the potentially infected total joint arthroplasty. Clin Orthop Relat Res 2014; 472: 406-409 [PMID: 25256621 DOI: 10.1007/s11999-014-3960-7]
Kasperek MF, Kasperek M, Boettner F, Faschingbauer M, Hahne J, Dominikus M. Intraoperative Epidemiology and new developments in the diagnosis of prosthetic joint infection. Int J Artif Organs 2012; 35: 923-934 [PMID: 23138706 DOI: 10.5301/ijao.5000168]
Sigmund IK, Holinka I, Gamber J, Staats K, Böhler C, Kubista B, Windhager R. Qualitative α-defensin test (Synovasure) for the diagnosis of periprosthetic infection in revision total joint arthroplasty. Bone Joint J 2017; 99-B: 66-72 [PMID: 28053259 DOI: 10.1302/0301-620X.99B1.BJJ-2016-0295.R1]
Kuiper JWP, Verberne SJ, Vos SJ, van Egmond PW. Does the Alpha Defensin ELISA Test Perform Better Than the Alpha Defensin Lateral Flow Test for PJI Diagnosis? Clin Orthop Relat Res 2020; 478: 1333-1344 [PMID: 32324670 DOI: 10.1097/CORR.0000000000001225]
Plate A, Stadler L, Sutter R, Anagnostopoulos A, Frustaci D, Zbinden R, Fucentese SF, Zinkernagel AS, Zingg PO, Achermann Y. Inflammatory disorders mimicking periprosthetic joint infections may result in false-positive α-defensin. Clin Microbiol Infect 2018; 24: 1212.e1-1212. e6 [PMID: 31781265 DOI: 10.1016/j.cmi.2017.11.001]
Abdo RCT et al. Alpha-defensin lateral flow with prior centrifugation

29 Partridge DG, Gordon A, Townsend R. False-positive synovial fluid alpha-defensin test in a patient with acute gout affecting a prosthetic knee. Eur J Orthop Surg Traumatol 2017; 27: 549-551 [PMID: 28314986 DOI: 10.1007/s00590-017-1942-8]

30 Adams JR, Schwartz AJ. False-negative synovial alpha-defensin. Arthroplast Today 2017; 3: 239-241 [PMID: 29204488 DOI: 10.1016/j.artd.2017.05.006]

31 Gehre T, Laumann C, Citak M, Bonanzinga T, Frommelt L, Zahar A. The Accuracy of the Alpha Defensin Lateral Flow Device for Diagnosis of Periprosthetic Joint Infection: Comparison with a Gold Standard. J Bone Joint Surg Am 2018; 100: 42-48 [PMID: 29298259 DOI: 10.2106/JBJS.16.01522]

32 Balato G, Franceschini V, Ascione T, Lamberti A, D'Amato M, Ensini A, Baldini A. High performance of α-defensin lateral flow assay (Synovasure) in the diagnosis of chronic knee prosthetic infections. Knee Surg Sports Traumatol Arthrosc 2018; 26: 1717-1722 [PMID: 28988303 DOI: 10.1007/s00167-017-4745-x]

33 Math KR, Scheider R. Imaging of the Painful TKR. In: Scuderi GR, Tria AJ, editors. Surgical Techniques in Total Knee Arthroplasty. New York, NY: Springer New York, 2002: 351-367
