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Results of the intraoperative alpha defensin lateral flow test in the second stage of revision hip arthroplasty

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Abstract

Background Alpha defensin lateral flow (ADLF) test is a current accurate tool for detecting/excluding periprosthetic joint infection (PJI); however, its usage in patients with a hip joint spacer has not yet been fully studied.

The **purpose** of the study was to determine the diagnostic parameters (accuracy, specificity, sensitivity, AUC) of the alpha-defensin lateral flow test as part of the reinfection verification in patients with a hip joint spacer in the second stage of revision hip arthroplasty (RHA).

Material and methods In a prospective study the effectiveness of the intraoperative use of ADLF test was evaluated in 105 patients with hip joint spacers during the 2nd stage of revision hip arthroplasty (RHA). The standard microbiological examination of intraoperative samples of tissues and synovial fluid was accepted as the gold standard for re-infection diagnosis.

Results The growth of microflora according to the results of intraoperative microbiological examination was detected in 24 (23 %) cases. The discrepancy in the results of intraoperative microbiological examination and the results of the ADLF test was found in 10 (11 %) cases. False positive and false negative cases were identified. ADLF test demonstrated 96.39 % specificity, 89.52 % accuracy and 63.64 % sensitivity. The AUC index was 0.8.

Discussion ADLF test has good diagnostic indicators for the verification of PJI in patients after hip replacement. The use of ADLF test in patients with a hip joint spacer who continue antibacterial therapy allows the test to be performed in the 2nd stage of RHA. However, the results of ADLF test in patients during the 2nd stage of RHA show that additional studies are required.

Conclusion The ADLF test, despite the divergent data from scientific publications, demonstrates high diagnostic value for intraoperative verification of reinfection in patients with a hip joint spacer, allowing timely correction of treatment tactics. "Dry tap", bloody synovial fluid, as well as weakly virulent coagulase-negative microflora, including in microbial associations, are limitations of the ADLF test application.

Keywords: periprosthetic joint infection (PJI), diagnosis of hip joint reinfection, intraoperative aspiration of synovial fluid of the hip joint, hip joint spacer, revision hip arthroplasty, alpha defensin lateral flow test (ADLF)

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INTRODUCTION

Total hip arthroplasty, being the “operation of the 21st century” [1], can significantly improve the quality of life of patients suffering from late stages of osteoarthritis [2]. Growing obesity rates and increasing life expectancy contribute to the growth of musculoskeletal diseases [3, 4]. As a result, the number of primary arthroplasties of large joints and the associated number of potential complications has been growing [5]. Periprosthetic joint infection (PJI) is one of the leading complications after joint arthroplasty in terms of incidence, destructiveness and cost of treatment [6, 7]. Timely and accurate diagnosis of periprosthetic infection of the hip joint allows for the most rational choice of treatment tactics and a reduction in the risk of potentially adverse consequences [8].

The "gold standard" for treating patients with chronic periprosthetic joint infection is two-stage revision hip arthroplasty (RHA), which involves removing the hip implant components, debridement, and installation of a spacer impregnated with antibacterial drugs at the first stage. After the infection process has been stopped, the wound has healed, and laboratory parameters have returned to normal, the second stage of RHA is performed, which involves removing the spacer, debridement, and re-implantation of components [9]. In any case, the authors report high rates of reinfection after the second RHA stage [10, 11]. In this regard, perioperative diagnosis to exclude reinfection during the second stage of RHA is an extremely important task. There are various algorithms for diagnosing PJI, such as ICM, WAIOT, EBJIS; each of them has good diagnostic value [12]. However, these algorithms to make a decision on performing the second revision stage have limited significance [13]. In the absence of a generally accepted preoperative diagnostic algorithm before performing the second stage of RHA, the use of various synovial intraoperative express tests becomes relevant, allowing exclusion or detection of reinfection and, if necessary, and changes in the treatment tactics.

Alpha-defensin lateral flow (ADLF) test is one of the most current, rapid, sensitive and specific tests that allow for effective verification of PJI, even in the context of ongoing antibacterial therapy [14, 15, 16]. Moreover, the updated ICM 2018 algorithm has added the determination of alpha-defensin proteins in synovial fluid as a “minor criterion” for diagnosing PJI [17]. However, there is currently insufficient data on how effective ADLF test is in detecting reinfection after spacer placement [18]. There is an opinion that the characteristics of local immunity after first-stage RHA operations, as well as the very presence of an installed spacer impregnated with antibacterial drugs, contribute to a decrease in the prognostic significance of using various serum and, especially, synovial biomarkers in order to exclude reinfection [19]. Available data on the assessment of ADLF test diagnostic parameters in the context of perioperative diagnosis of reinfection during the second stage of revision hip arthroplasty in patients with an installed hip spacer vary significantly [20, 21, 22, 23].

The **purpose** of the study was to determine the diagnostic parameters (accuracy, specificity, sensitivity, AUC) of the alpha-defensin lateral flow test as part of reinfection verification in patients with a hip joint spacer in the second stage of revision hip arthroplasty (RHA).

MATERIALS AND METHODS

A total of 135 patients took part in a prospective study conducted in 2019–2024 at the Orthopaedic Department of the Botkin City Clinical Hospital.

Inclusion criteria:

— a hip spacer installed for the first time due to periprosthetic infection;

— no clinical signs of an infectious process in the area of the planned operation (no fistula, local hyperemia, hyperthermia);

— consent to perform the second stage of revision arthroplasty;

— written informed consent to participate in the study.

Non-inclusion criteria:

— active infectious process with the presence of a fistula in the hip joint area, local hyperemia, hyperthermia;

— patients with a previous Girdleston operation ("hanging hip") for periprosthetic infection;

— objective contraindications to revision surgery due to somatic or mental status;

— presence of HIV infection;

— patients with repeated spacer implantation.

Exclusion from the study:

— the patient develops a fistula in the area of the hip joint;

— the patient refuses surgery and does not want to participate in the study;

— reinfection is detected during preoperative diagnostic examination;

— the patient dies before the second stage of RHA is performed.

The study assessed the diagnostic parameters of intraoperative alpha-defensin lateral flow test in patients with an installed hip spacer during the second stage of RHA.

The average age of patients was 64 years (42–78 years). Most patients included in the study were women (n = 67; 63 %), while 38 patients (37 %) were men. The average time to the second stage of RHA was 45 weeks (19–69).

All 135 (100 %) patients admitted for the second stage of RHA were pre-examined to exclude reinfection in the hip joint. As part of the pre-operative exclusion of reinfection, serum biomarkers (ESR, CRP, leukocyte count in the general blood test, interleukin-6) were analyzed and pre-operative aspiration of synovial fluid of the examined hip joint was performed with subsequent microbiological analysis of the aspirate.

During preoperative examination, 26 (19 %) cases of microflora growth were detected (according to the results of preoperative microbiological testing during preoperative synovial fluid aspiration). The situation was interpreted as reinfection. Those patients were excluded from the study and referred for repeated sanitation and hip joint spacer change.

There were also 4 (3 %) cases of fistula developed in the area of the involved hip joint detected before the second stage of RHA. The situation was interpreted as the fistula form of reinfection. Those patients were also excluded from the study and referred for debridement and hip joint spacer change (Fig. 1).

According to preoperative diagnostic examination, reinfection was excluded in 105 (78 %) patients. All 105 patients admitted for the second RHA stage were required to cease the intake of antibacterial drugs at least 14 days before the date of the planned operation (the so-called "antibacterial holidays").

The second RHA stage included removal of the spacer, sanitation and reimplantation of revision components. In all patients, peri-implant tissue samples were taken from the joint cavity and from under the removed spacer components (from 3 to 6 samples) upon approach to the joint and after explantation of the spacer. The samples were then subjected to microbiological analysis with a cultivation period of 14 days and mandatory determination of sensitivity to antibacterial drugs in case microorganism growth was detected.

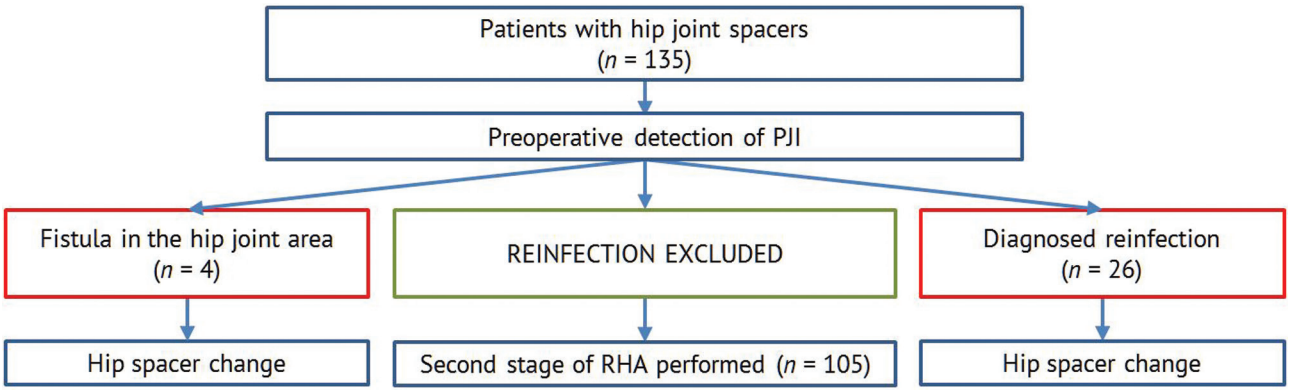

Fig. 1 Diagram of study design

At the stage of approaching to the spacer before opening the fascia, synovial fluid was aspirated in all patients for further microbiological examination. Cultivation was performed on the PEDS PLUS nutrient medium and continued 14 days. If there was a sufficient volume of synovial fluid (at least 5 ml) without visible traces of blood and/or other impurities, an express test for alpha-defensin was performed for the purpose of intraoperative verification of reinfection.

Intraoperative administration of antibacterial drugs was performed only after sampling of peri-implant tissues and synovial fluid. If the operation lasted for 2–4 hours or more, an additional dose of antibacterial drugs was administered in accordance with clinical recommendations (depending on the drug administered) [24].

In the absence of synovial fluid during intraoperative aspiration ("dry joint"), the patient was prescribed a course of two-component empirical antibacterial therapy until the results of the intraoperative microbiological study of peri-implant tissue samples were obtained. In the absence of microflora growth according to the results of the intraoperative microbiological study, the course of antibacterial therapy was canceled in the second stage of revision arthroplasty.

The results of intraoperative microbiological analysis of peri-implant tissue samples and synovial fluid during the second RHA stage were used as references, on the basis of which the results of intraoperative verification of reinfection using the alpha-defensin express test were assessed and analyzed.

The implementation of the alpha-defensin express test and the interpretation of the results obtained were in accordance with the manufacturer's instructions (Fig. 2).

The intensity of the control line and the test strip result on the device may vary. Any solid reddish-pink line is considered a line, regardless of intensity or size. Test results should not be interpreted after 20 minutes.

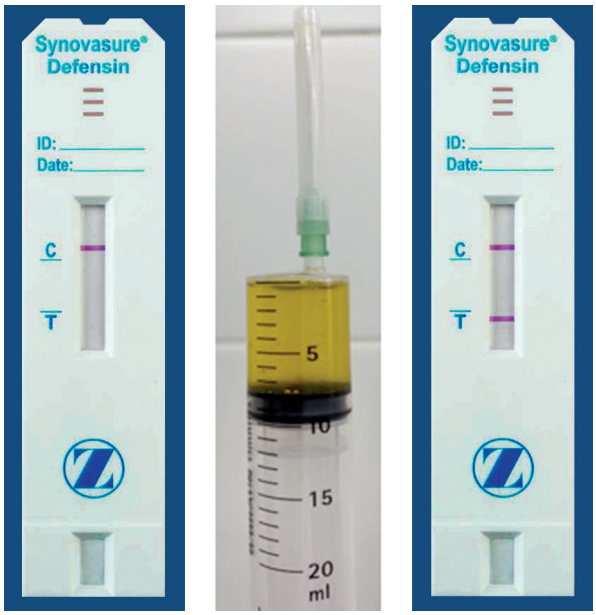

Fig. 2 Illustration of the results of the alpha-defensin express test: left — negative result; center — sample of the synovial fluid used, right — positive result [1]

[1] https://www.zimmerbiomet.com/content/dam/zb-corporate/en/products/specialties/diagnostics/synovasure-alpha-defensin-lateral-flow-test/1314.2-GLBL-en-Synovasure-Reference-Guide.pdf

A *negative result* for alpha defensin means only the presence of a reddish-pink control line (C) on the device without the appearance of a result on the test strip (T) after 10 min. The presence of a control line indicates that the test was performed correctly.

A *positive (non-negative) result* for alpha defensin is the appearance of a reddish-pink control line (C) on the device and a reddish-pink line on the test strip (T). The presence of the control line indicates that the test was performed correctly.

Invalid test Before interpreting the results, it is checked whether the control line marked "C" has appeared on the device. If the control line does not appear, the test strip does not appear completely, or the background does not become clear, the test is considered invalid and the results cannot be used. The test should be repeated with a new device. For retesting, use the previously prepared dilution vial. The retest should be performed within 4 hours.

In case of a positive result, the patient was prescribed a course of two-component empirical antibacterial therapy until the results of a intraoperative microbiological study were obtained. If there was growth of the patient's microflora, the patient was prescribed antibacterial based on the sensitivity data of the identified microorganism.

The study was conducted in accordance with the "Rules of Clinical Practice in the Russian Federation" (Order of the Ministry of Health of the Russian Federation dated June 19, 2003, No. 266), the ethical principles of the Helsinki Declaration (World Medical Association Declaration “Ethical Principles for Medical Research Involving Human Participants”, 2013) and with the approved by the ethics committee at the First Sechenov Moscow State Medical University (protocol dated January 20, 2022, No. 01-22).

Microsoft Office Excel was used to collect, process and systematize the information. Student's T-test was used to determine the statistical significance of the data. Differences at a significance level of $p < 0.05$ were considered statistically significant. The data were also analyzed using MedCalc 13.2.2 (MedCalc Software bv, Ostend, Belgium) to conduct ROC analysis and determine the sensitivity, AUC, specificity and accuracy of the alpha-defensin express test of intraoperative verification of reinfection in patients with a hip spacer.

RESULTS

According to the results of microbiological examination of intraoperative peri-implant tissue samples and synovial fluid at the second stage of revision hip arthroplasty, 24 cases (23 %) of microflora growth were identified (Fig. 3).

The following data were obtained regarding the results of intraoperative verification of reinfection using the alpha-defensin express test: out of 105 patients who underwent revision surgery, the effectiveness of this test could be assessed in 86 (82 %) cases (Fig. 4).

In 3 (3 %) patients, synovial fluid with a high content of associated blood was obtained by intraoperative aspiration. In the remaining 16 (15 %) patients, no synovial fluid could be obtained by intraoperative synovial fluid aspiration (“dry tapt”). This fact indicates that it was impossible to assess the effectiveness of any synovial biomarkers in 18 % of cases (Fig. 4).

The diagnostic indicators of the alpha-defensin lateral flow express test in cases of sufficient synovial fluid material without foreign impurities are presented in the diagram (Fig. 5).

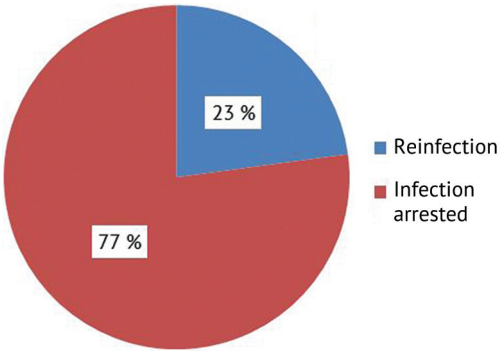

Fig. 3 Results of intraoperative microbiological examination of peri-implant tissue samples and synovial fluid

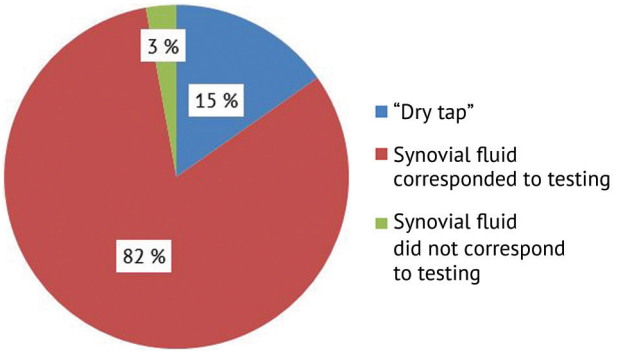

Fig. 4 Distribution of patients according to intraoperatively obtained aspirate

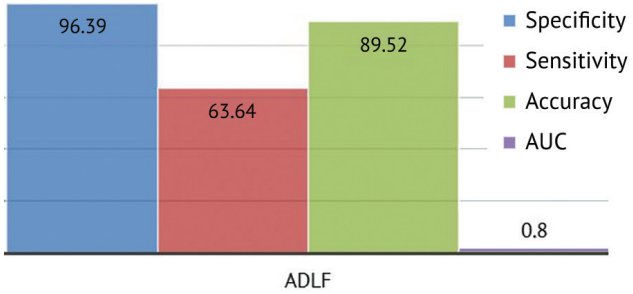

Fig. 5 Diagnostic indicators of intraoperative use of alpha-defensin express test in patients with an installed hip joint spacer

According to the results of the intraoperative microbiological examination of peri-implant tissue and synovial fluid samples, 65 (76 %) true negative and 11 (13 %) true positive results of the ADLF test were obtained.

Also, there were 10 (11 %) cases in which a discrepancy was observed between the results of the intraoperative ADLF test and the microbiological examination of intraoperative peri-implant tissue and synovial fluid samples: false negative result in 7 cases (7 %), false positive result in 3 cases (4 %).

No statistically significant differences were found in the analysis of the obtained results of the microbiological examination of intraoperative peri-implant tissue and synovial fluid samples when compared with the results of the intraoperative alpha-defensin express test ($p \geqslant 0.05$).

DISCUSSION

A study devoted to the specific effects of articulating spacers on peri-implant tissues revealed that spacers made of PMMA promote an immunomodulatory effect on the synovial membrane and tissues surrounding the implant. The membrane formed at the spacer-bone contact is induced by various immune cells (due to cement abrasion, formation of cement debris, and migration of cellular immunity components) [29]. It is important to understand that antibacterial drugs impregnated in the spacer are released into the synovial fluid and contribute to false-negative results of microbiological testing [30].

The duration of antibacterial release from the spacer is quite debatable. In this regard, the accuracy of synovial biomarkers in the aspirated synovial fluid in patients with an installed spacer may differ at different time-points. Thus, Boelch et al. demonstrated that the local concentration of antibacterial drugs may remain elevated for more than 6 weeks from the time of surgery. The authors state

that the findings were obtained in an *in vitro* experiment, and that in *in vivo* situations the duration of antibiotic release may differ [31]. Based on the above, the presence of an elevated concentration of immune cells and antibacterial drugs in the joint cavity may contribute to false results of reinfection diagnosis in synovial fluid studies.

Despite the abundance of various serum and synovial markers of periprosthetic joint infection, the diagnostic accuracy of synovial tests exceeds serum biomarkers [25]. However, synovial fluid cannot be obtained by pre/intraoperative aspiration in all cases. Therefore, it is impossible to evaluate the effectiveness of any synovial biomarkers for the purpose of verifying PJI/reinfection in about a third of cases [26, 27]. In our study, the number of cases in which ADLF test was not performed due to the absence/extremely scarce amount of synovial fluid or due to the fact that it did not meet the criteria for ADLF test during intraoperative aspiration was 18 %.

The high efficiency of the alpha-defensin test for verification of periprosthetic infection in large joints has been proven [28, 29, 30, 31, 32]. In turn, there are few publications evaluating the diagnostic potential of the alpha-defensin express test in the context of excluding/confirming reinfection in patients with an installed hip spacer.

Carender et al. evaluated the diagnostic value of preoperative use of alpha-defensin express test in patients with installed spacers in knee and hip joints before performing the second stage of revision arthroplasty [22]. The authors demonstrated data on high specificity (96 %) with 0 % sensitivity of the method, indicating that the alpha-defensin test did not increase the efficiency of preoperative exclusion of reinfection when added to the generally accepted synovial and serological markers of infection detection [22].

In other studies, the authors found high diagnostic rates of the alpha-defensin express test before performing revision arthroplasty [21, 33]. In the study by Frangiamore et al., the specificity and sensitivity rates of the method were 97 % and 67 %, respectively [33]. Stone et al. also reported high specificity (92 %) with less significant sensitivity (50 %) rates using the alpha-defensin express test in patients with an installed spacer before performing the second stage of revision arthroplasty [21].

The authors draw attention to two false-negative results of the alpha-defensin express test, noting the growth of *Cutibacterium acnes* in one case and the detection of the growth of two different coagulase-negative staphylococci (microbial association) in the second case [21].

It should be emphasized that neither Stone et al. nor Frangiamore et al. indicated the number of "dry tap" in their works, and therefore the true indicators of the effectiveness of the alpha-defensin test in patients with an installed spacer in those publications remain unclear [21, 33].

Our study also revealed seven cases of false-negative results of the alpha-defensin rapid test, associated with the growth of various weakly virulent coagulase-negative microorganisms in 5 cases (71 %) and in 2 cases (29 %) with the detection of various microbial associations. The false-negative results of the ADLF test that we obtained are consistent with the causes of false-negative results in other studies [21, 34, 35].

The false-positive results of the alpha-defensin test (3 cases, 4 %) obtained in our study are most likely associated with the use of fluid that did not fully meet the criteria for performing the test: the synovial fluid obtained by intraoperative aspiration contained a hemorrhagic component (Fig. 6).

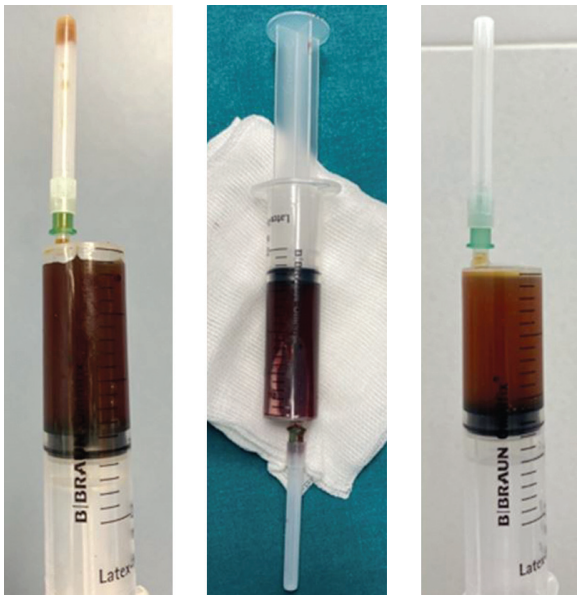

Fig. 6 Intraoperatively obtained samples of synovial fluid with a hemorrhagic component

Some publications report the successful use of alpha defensin test for synovial fluid containing blood admixture, in contrast to the use of test strips for determining leukocyte esterase [36, 37]. However, the authors did not specify the volume of dilution/blood admixture in those tests.

The instructions for use provide a conclusion on the high diagnostic value of alpha-defensin express test, but there is a note that the indicators are relevant to using synovial fluid samples, excluding samples with blood dilution > 20 % [2]. In this regard, the probability of obtaining false positive results of alpha-defensin test for using synovial fluid with more than 20 % blood dilution is not excluded.

According to the results of our study, the diagnostic accuracy rates of intraoperative use of ADLf test in the context of reinfection verification in patients with an installed hip spacer were 96.39 % for specificity and 63.64 % for the sensitivity of the method, which is similar to the results of similar studies [21, 33].

Shahi et al. claim that such a diagnostic tool for periprosthetic joint infection as alpha-defensin had a higher specificity and provided better screening for PJI in patients continuing to take antibacterial drugs than serum ESR, CRP, determination of PMN in synovial fluid, and even microbiological testing [16]. However, the study was conducted before revision surgery, and it is not possible to evaluate the effectiveness of this tool in patients with an installed spacer. In turn, Owens et al. noted that the routine use of such a synovial biomarker as alpha-defensin before performing the second stage of RHA may be unjustified [38].

Treatment of PJI is a complex task that requires a multidisciplinary approach and an experienced team of specialists, including a clinical pharmacologist [39]. Despite the fact that there is currently no single protocol for prescribing antibacterial therapy in the second stage of revision arthroplasty, it is important to understand that antibiotics should be selected based on the patient's somatic condition (kidney function, liver function, cardiovascular system), taking into account possible allergic reactions to a particular antibacterial drug, as well as the results of microorganism sensitivity according to the microbiological study conducted during the first stage of RHA. Patients admitted for the second stage of RHA are preliminarily examined, reinfection/relapse of PJI should be excluded. Such patients are recognized as "reconvalescents" for PJI. Therefore, it is relevant to use preventive, rather than therapeutic regimens and dosages when prescribing antibacterial drugs.

[2] https://www.zimmerbiomet.eu/en/products/synovasure-alpha-defensin-lateral-flow-test#overview

Different medical centers use different empirical schemes that are based on the characteristics of the species spectrum of pathogens causing PJI and local treatment protocols [40]. Most often, various combinations or monotherapy with antibacterial drugs of such groups as third-generation cephalosporins, glycopeptides, lincosamides, fluoroquinolones [41], as well as broad-spectrum beta-lactams [42] are used.

In intraoperative verification of reinfection/relapse of PJI from the samples of peri-implant tissues from the joint cavity and from under spacer components removed, as well as a sample of synovial fluid, followed by ADLF test (if SF meets the test performance criteria), a prophylactic dose of one of the antibacterial drugs was administered for two days in case of a negative ADLF result. If a positive ADLF result was obtained, two antibacterial drugs were administered intraoperatively (as part of the initial empirical therapy) until the results of the intraoperative microbiological study were obtained, followed by a transition to targeted prolonged antibacterial therapy, based on the sensitivity data.

CONCLUSION

Like all synovial biomarkers, ADLF test is ineffective in "dry tap". The test also demonstrates limited results if synovial fluid with a pronounced hemorrhagic component is used and in the presence of weakly virulent coagulase-negative microflora and/or microbial associations.

Alpha-defensin lateral flow test demonstrated high rates of diagnostic accuracy, specificity and AUC in patients with a hip spacer at the second stage of RHA. ADLF test is a good additional intraoperative express test, allowing, if necessary, correction of treatment tactics. Despite conflicting data from scientific publications, the use of ADLF test allows for effective verification of reinfection and is a good tool for confirming successful eradication of hip joint infection.

Conflict of interest *Not declared.*

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