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"Unexpected" Infections in Revision Arthroplasty for Aseptic Loosening

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Abstract

Background. Data from the national registers of arthroplasty showed that about 12% of hip and knee arthroplasty undergo revision within 10 years after the primary surgery. The leading cause of hip revisions is aseptic loosening of components, knee joint — periprosthetic infection (PPI). Some of the infectious complications, including those related to mechanical causes, remain out of sight. ***The aim of the study*** was to identify the frequency of «unexpected» infections during revision knee and hip arthroplasty performed for aseptic complications of any etiology. ***Materials and Methods.*** 839 cases of revision arthroplasty of knee and hip joints were analyzed, including 485 aseptic revisions in 450 patients. Clinical, X-ray, laboratory (complete blood count and comprehensive metabolic panel, coagulation panel) methods, synovial fluid analysis and microbiological examination of punctures, including intraoperative ones, were used. The ICM and EBJIS (European Bone and Joint Infections Society) consensus recommendations were used as criteria for assessing the presence of infection. ***Results.*** The average age of patients at the time of the revision was 61.7 years. The hip joint prevailed (59.4%), knee joint — 40.6%. The growth of microorganisms in the intraoperative biomaterial was detected in 2.08% of observations: in 10 out of 287 patients after aseptic revision of the hip joints and in none of the 198 revisions of the knee joints. In 8 out of 10 cases, the causative agents were coagulase-negative staphylococci, including 6 — MRSE; in two cases, anaerobic bacteria. All revisions were carried out by a one-stage method. Patients with detected PPI underwent systemic antibacterial therapy. At the stage of catamnesis, reinfection was assumed in one of the 10 identified cases of PPI, the patient did not show up for revision. In control 63% of the group of the other (aseptic) 470 patients, PPI developed in 4 cases, two-stage revisions were carried out. ***Conclusions.*** The frequency of infections accidentally detected during aseptic revisions of large joints was 2.08%. Three-time examination of joint punctures, including intraoperative, provides additional opportunities for the diagnosis of PPI during aseptic revision, and also allows you to choose the optimal stage of revision treatment. The experience gained makes it possible in certain cases to perform one-stage revision in the treatment of PPI.

Keywords: arthroplasty, revision arthroplasty, aseptic revision, periprosthetic infection, joint puncture, microbiological analysis.

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«Неожиданные» инфекции при асептических ревизиях

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Реферат

Актуальность. Данные мировых регистров артропластики суставов показали, что около 12% эндопротезов тазобедренного и коленного суставов подвергаются ревизионным вмешательствам в течение 10 лет после первичной операции. Лидирующая причина ревизий тазобедренного сустава — асептическое расшатывание компонентов, коленного — перипротезная инфекция (ППИ). Часть инфекционных осложнений, в т.ч. связанных с механическими причинами, остается вне поля зрения врачей. ***Целью работы*** является выявление частоты «неожиданных» инфекций при ревизионном эндопротезировании коленных и тазобедренных суставов, выполненном по поводу асептических осложнений любой этиологии. ***Материал и методы.*** Проанализировано 839 случаев ревизионного эндопротезирования коленного (КС) и тазобедренного (ТБС) суставов, в том числе 485 асептических ревизий у 450 пациентов. Применялись клинический, рентгенологический, лабораторный (общий и биохимический анализы крови, коагулограмма) методы, анализ синовиальной жидкости и микробиологическое исследование пунктатов, в т.ч. интраоперационных. В качестве критериев оценки наличия инфекции использовали рекомендации консенсуса ICM и EBJIS (Европейского общества по инфекциям костей и суставов). ***Результаты.*** Средний возраст пациентов на момент ревизии составил 61,7 года. На ТБС выполнено 59,4% ревизионных операций, на КС — 40,6%. Рост микроорганизмов в интраоперационном биоматериале обнаружен в 2,08% наблюдений: у 10 из 287 пациентов после асептической ревизии тазобедренных суставов и ни в одном случае из 198 ревизий коленных суставов. В 8 из 10 случаев возбудителями были коагулазо-негативные стафилококки, в том числе в 6 — MRSE; в двух случаях — анаэробные бактерии. Все ревизии проведены одноэтапным методом. Пациентам с обнаруженной ППИ проведена системная антибактериальная терапия. На этапе катамнеза в одном из 10 выявленных случаев ППИ предполагалась реинфекция, пациент на ревизию не явился. При контроле 63% из группы остальных (асептических) 470 пациентов в 4 случаях развилась ППИ , проведены двухэтапные ревизии. ***Заключение.*** Частота инфекций, случайно обнаруженных при асептических ревизиях крупных суставов, составила в 2,08%. Трехкратное исследование пунктатов сустава, в т.ч. интраоперационных, предоставляет дополнительные возможности диагностики ППИ при асептической ревизии, а также позволяет избрать оптимальную этапность ревизионного лечения. Полученный опыт позволяет в определенных случаях при лечении ППИ выполнять одноэтапное реэндопротезирование.

Ключевые слова: ревизионное эндопротезирование, перипротезная инфекция, асептические ревизии, пункция сустава, микробиологическое исследование.

Источник финансирования: исследование проведено без спонсорской поддержки.

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Background

The increase in the number of primary arthroplasties in recent years has led to a significant increase in revision interventions worldwide [1, 2, 3, 4, 5, 6]. Data from the national arthroplasty register (AR) showed that about 12% of hip and knee endoprostheses undergo revision within 10 years after the initial surgery [7, 8, 9].

The most common cause of revision total hip arthroplasty (THA) is aseptic loosening of components — 34-94% of cases. This is followed by deep infection, recurrent dislocations, mechanical destruction of implants, periprosthetic fractures [1]. Thus, the most common reason for revision after THA in the period up to 1.7 years is periprosthetic joint infection (PJI), while later, aseptic instability and wear of the endoprosthesis components (wear of the insert) prevail among the indications for revision THA [10].

For the knee, the most common cause of revision is infection (36.1%), followed by aseptic loosening (21.9%) and periprosthetic fracture (13.7%) [11].

V.I. Roberts et al. report that PJI is the second most common cause of implant failure after aseptic loosening of endoprosthesis components [7].

However, infection rates are probably actually underestimated, since many cases of suspected aseptic loosening of the endoprosthesis can be caused by an unrecognized infection [7, 10]. It is often difficult to determine the exact cause of functional instability (septic or aseptic) in such patients [12].

The main problem of revision arthroplasty is the lack of a reliable and valid pre- and intraoperative diagnostic tool with 100% specificity and 100% sensitivity in the diagnosis or exclusion of PJI [13,14]. The available diagnostic search methods are not informative enough, which leads to delayed diagnosis, and the diversity of views on the surgical treatment of PJI indicates the relevance of a unified approach to the diagnosis and treatment of this pathology [15]. Along with the annual increase in the number of revision surgery, there is also a growing need to develop a technique for differential diagnosis between aseptic loosening of the implant and instability with the addition of microbial agents.

Currently, various criteria and algorithms are used for the diagnosis of PJI, including those developed at the International Consensus Meeting in 2013 and then at the Second International Consensus Meeting on Musculoskeletal Infection (International Consensus Meeting — ICM, 2018) [16, 17], as well as criteria and algorithms proposed by the The European Bone and Joint Infection Society — EBJIS [18]. However, in some cases, PJI can be caused by low-virulent microorganisms, for example, Propionibacterium acnes, when the listed criteria are unacceptable [8, 12, 14, 18, 19, 20].

In some studies were mentioned patients in whom the cause of aseptic revision arthroplasty may have been PJI [8, 14, 19, 21, 22]. Not every case of PJI meets the criteria described above. In addition, any identified mechanical causes may be combined with a chronic infection, which must be taken into account during the examination [19].

Currently, there is no absolute test for the diagnosis of PJI, which forces clinicians to rely on a combination of studies of synovial fluid and serological markers, which are an equally important in diagnostic [23]. Timely and accurate diagnosis of PJI is crucial for planning appropriate treatment tactics. It is extremely important to exclude infection as a possible etiological factor in the preoperative period, since the tactics of surgical treatment vary depending on the causes of the revision. Some orthopedic surgeons prefer one-stage revision in the treatment of late PJI [24, 25], others prefer two-stage revision arthroplasty [26, 27, 28].

The aim of the study was to identify the frequency of "unexpected" infections during revision total arthroplasty of the knee and hip joints performed for aseptic complications of any etiology.

Materials and methods

We conducted a retrospective continuous single-center study of all cases of aseptic revision total arthroplasty of knee and hip joints performed at the Federal State Budgetary Institution "Federal Center of Traumatology, Orthopedics and Endoprosthetics" of the Ministry of Health of Russia (Cheboksary) (hereinafter referred to as the Center) in 2017–2019. The data of electronic medical records of patients in the medical information system (MIS) are analyzed. Informed consent to personal data processing was obtained from all patients.

Previous operations of total knee arthroplasty (TKA) and THA were performed in the conditions of the Center, also in other medical organizations of the Russian Federation and abroad. All aseptic revisions at the Center were carried out by a one-stage method. It should be noted that when PJI is detected, the Center mainly uses two-stage revision (removal of all infected components, spacer implantation, antibiotic therapy, the second stage of revision).

The main criterion for the presence of infection in the joint in the case of revision for a complication of presumably aseptic etiology were the positive results of bacteriological examination of intraoperative samples — the growth of identical microorganisms in two or more samples when detecting low-virulent microorganisms; in one sample — when detecting high-virulent pathogens.

The diagnostic algorithm included measures to identify the infectious process based on the complex application of clinical, laboratory and instrumental tests. Before hospitalization, patients were recommended to perform X-rays, CT and ultrasound exami-

nation of the joints (according to indications). Upon admission to the hospital, anamnesis data were studied in detail, clinical examination, physical examination were performed, local status was described, X-ray and laboratory tests were performed.

Laboratory screening included a study of the total blood count with erythrocyte sedimentation rate (ESR), a biochemical blood test with the determination of C-reactive protein (CRP), a coagulogram with D-dimer; synovial fluid analysis with the count of leukocytes and the percentage of polymorphonuclear neutrophils.

The ESR study was performed from venous blood using the Westergren method using an automatic Vital Mix-Rate X100 analyzer and MONOSED test tubes (Vital Diagnostics, Italy). CRP and D-dimer were measured in blood serum/plasma by immunoturbidimetric method.

Before the revision surgery, patients underwent joint punctures, with at least one of them in the Center (the total number of required punctures is usually three). Aspiration of synovial fluid from knee joint was performed under aseptic conditions without the use of local anesthetics, from hip joint — with the use of anesthetics and with ultrasound navigation. In the future, the count of the leukocytes number, leukocyte formula and microbiological examination of the punctate were carried out.

The study was carried out even if the volume of the aspirate received was less than 1 ml. The samples had the form of a non-complete punctate or were hemorrhagic in nature with additional notes "hemorrhagic sample", "flushing".

The study of synovial fluid included the counting of nucleated cellular elements and the study of a Romanovsky–Giemsa stained smear in order to determine the proportion of neutrophilic leukocytes. With a small amount of material, a binocular microscope and plastic slide-tablet cameras were used to count the cellular elements of the synovial fluid. To count the cellular elements in biological fluids, they were examined in 20-fold dilution with isotonic or hypotonic sodium solution. If there was enough synovial fluid and it did not contain foreign impurities (wear particles), the SYSMEX XN-1000 series hematological analyzer was used in automatic analysis mode; the aspirate was cultured in vials of the BacT/ALERT3D bacanalyzer. In case of insufficient punctate volume, culture was carried out in a routine way — in broths prepared in the laboratory with culturing on nutrient media: columbian, chocolate, Schaedler agar.

During the surgery, aspirate was taken from the joint cavity and tissue biopsies. In 100% of cases of implant removal, they were examined. Aspiration (if the joint was not dry) was performed before dissection the joint capsule with a syringe for 5 minutes. The intraoperative punctate was delivered to the laboratory for leukocyte count. The leukoformula was analyzed only at elevated leukocyte levels. The result was reported to the operating room by phone in 10–15 minutes.

Intraoperatively, 4—6 tissue biopsies were taken from at least 4 different points, as well as joint fluid (if available). To isolate microorganisms from microbial biofilms, the removed endoprosthesis components were processed in a BRANSON 8510 ultrasound machine (USA) for 5 minutes at a frequency of 40 ± 2 kHz, followed by culturing of flushes on nutrient media. On average, 7 samples of the material were taken intraoperatively. All cultures were incubated up to 14 days, creating the necessary conditions for cultivation. The negative result was verified on the 7th and 14th days, positive — as the culture grows. When the growth of microorganisms was detected, the identification of pathogens with the determination of sensitivity was performed on an automatic bacteriological analyzer Vitec 2-compact (Bio Merieux, France).

Histological examination of joint tissues also allows to reveal the picture of nonspecific inflammation with the presence of neutrophil granulocytes, however, this study is not carried out at the Center. The main ("big") clinical and laboratory signs of PJI were considered to be two positive results of culturing with identical microorganisms. The level of CRP in blood plasma is more than 10 mg/l; ESR >30 mm/hour; D-dimer >860 ng/ml, an increase in the level of leukocytes in synovial fluid >2000 cells/ml, an increased percentage of polymorphonuclear neutrophils >70% were regarded as additional ("small") diagnostic signs of PJI [18, 29].

The study was conducted in three stages: at the 1st stage — preliminary selection of all cases of revision in the MIS with the exception of septic revisions (including one-stage and both stages of two-stage) and re-revisions; at the 2nd stage — sorting of observations cases on the affected joint with the exception of cases of revisions conducted on the 2nd-7th day after the primary arthroplasty during one hospitalization, as well as cases when microbiological examination of intraoperative materials was not carried out; at the 3rd stage — analysis of the data obtained and their statistical processing.

A total of 839 revisions were carried out during the study period (Fig. 1).

At the 1st stage, all cases of infection or suspicion of it detected before or during the surgery were excluded from the study (n = 354). In 120 observations at the first stage of the two-stage revision, 56 (46.7%) cases were initially characterized by "large" signs of PJI (the presence of a fistula — 29 and/or two positive cultures — 27 cases). In 33 (27.5%) cases there were "small" signs. In the remaining 31 cases (25.8%), it was necessary to confirm the PJI by performing additional punctures. During the third puncture, the growth of

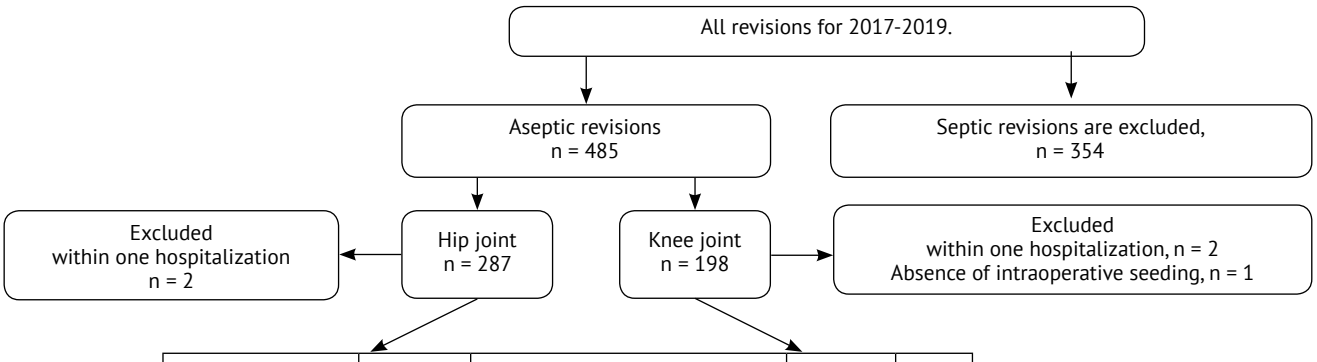
microorganisms was detected in 8 cases (6.7%). In two cases, with three negative preoperative punctures against the background of cytosis detected during the surgery, the growth of the pathogen in the intraoperative material was detected (1.7%). Along with this, in 5 cases (12.5%), positive punctures received before surgery were not confirmed by intraoperative culturing; in 16 cases, all punctures performed, including intraoperative ones, were culture-negative (13.3%), however, all described cases of PJI were confirmed clinically and laboratory and excluded from our study.

At the 2nd stage, 5 cases of revisions were excluded from the study. The remaining cases of aseptic revisions (n = 480) performed by one-stage method were distributed by types of non-infectious complications and analyzed in accordance with the evaluation criteria.

Demographic data (age, gender of patients and the affected joint); the time interval between primary arthroplasty or the revision/re-revision stage and the last revision were analyzed; the reasons for the revision; comparative data of biomaterials microbiological studies; the results of preoperative synovial fluid examination were evaluated. The clinical outcome in the medium term in patients with positive microbiological culturing was evaluated actively (by phone); the results of the surgery in other patients — as they applied to the Center at the stage of catamnesis.

Statistical analysis

Statistical processing of the obtained data was carried out using the analysis package of the Microsoft Excel 2007 program. The correspondence of the sample values to the normal distribution in MS Excel was confirmed graphically, which allowed reflecting the results in the form of arithmetic mean (M) and standard error (m), and in the absence of normality — minimum, maximum, median, mode. The Graph pad program was used to evaluate the statistical significance of differences in the frequency of deviations of laboratory parameters from the threshold values during THA and TKA. To assess the statistical significance of the frequency differences in the groups, an accurate Fisher test was used — it was calculated using the Graf Pad program. The differences were considered statistically significant at $p<0.05$.



Pathogen isolated, n = 10	Hip joint n = 285	Types of infectious complications	Knee joint n = 195	Pathogen was not identified
8	96	Aseptic loosening	117	
–	131	Liner wear	10	
2	58	Mechanical (fracture, dislocation, etc.)	43	
–	–	Joint instability	25	

Fig. 1. Study design flowchart

Results

The average age of patients at the time of the revision was 61.7 years (CI = 95%; SD = 10.1), among them there were 308 women (64.2%), 172 men (35.8%). In the study group, the failed THA prevailed (59.4%), TKA — 40.6%.

The sample size was 450 patients, the volume of studies — 480 revisions (including 17 repeated revisions on one joint, 13 bilateral surgeries in the same patient). There were no clinical signs of infection before surgery in all patients.

After primary arthroplasty, revisions were carried out in 447 cases (hip joint = 264 and knee joint = 183), including 14 (7.2%) cases — after unilateral knee arthroplasty. In 33 cases out of 480 (6.9%) patients had previously undergone revision surgery (including outside the study period).

In the structure of non—infectious complications that caused the revision, insert wear was the leader in the hip joint group (46%), aseptic instability in the knee joint group (60%).

The average period from the moment of surgery to the present revision was 6.4 years (SD = 3.8; Me = 6.8; Mo = 9.2; 0.1–19.3) The time interval from the previous surgery to current revision was 4.1 years for knee joint (SD = 2.7; Me = 3.9; Mo = 3.0; 0.1–15.0), for hip joint — 8.1 years (SD = 3.6; Me = 8.6; Mo = 9.2; 0.1–19.3).

The obtained results of the blood test revealed a significant number of inflammation biomarkers deviations from the threshold values (Table 1).

The frequency of deviations from the threshold values in patients with aseptic revision of knee joint was 12.7% for CRP, 37.9% for D-dimer and 11.2% for ESR; with aseptic revision of hip joint: 17.9% for CRP, 41.8% for D-dimer and 11% for ESR.

The relationship between the frequency of detected deviations of laboratory parameters in patients with aseptic revision of knee joint and hip joint was not statistically significant: for CRP — p = 0.2067, for D-dimer — p = 0.4324 and for ESR — p = 1.0.

The analysis of synovial fluid with the count of leukocytes and the percentage of polymorphonuclear neutrophils in the pre- and intraoperative periods showed a predominance in the frequency of three-time punctate examination.

Punctates of 91.2% of patients were examined at the preoperative period, 76.8% intraoperatively. The positive results of preoperative punctations performed at the place of residence in 6 cases did not coincide with the results obtained at the Center and were recognized as false positive.

Punctates of 91.2% of patients were examined at the preoperative period, 76.8% intraoperatively. The positive results of preoperative punctations performed at the place of residence in 6 cases did not coincide with the results obtained at the Center and were recognized as false positive.

Aspirate sampling with different time intervals was performed three times in 67.7% of cases, twice in 13.1% and once in 10.4%. At the outpatient stage, punctates of 8.75% of patients with mechanical complications (dislocation or periprosthetic fracture) detected by X-ray method were not examined. Subsequently, in some of these patients, the punctate was obtained intraoperatively. At the same time, 4.9% of the total number of patients (n = 480) were not punctated either before or during surgery.

The studied group of patients underwent 804 joint punctures (hip joint + knee joint) in the polyclinic of the Center. Of these, 32.6% of the results showed the presence of hemorrhagic contents in the punctate, which may be due to both the presence of blood in the joint cavity and traumatization of the vessel during the manipulation. 13.9% of the studies were possible only by diluting the punctate with saline ("dry" joint). At the same time, a difference in the quality of the received punctates was revealed, probably related to the complexity of taking biomaterial due to anatomical features of approach to the joint. 26.8% of knee joint punctates (95 out of 354) and 44.9% of hip joint punctates (202 out of 450) did not meet the requirements of cytological examination.

The results of bacteriological examination of synovial fluid before surgery in all patients (hip joint and knee joint) were negative, while some laboratory parameters did not allow to completely exclude PJI.

Out of 480 cases of aseptic revision, "unexpected" positive intraoperative cultures were found in 10 cases, which amounted to 2.08% of the total number of studies conducted (Table 2).

A positive result with identical sensitivity was obtained in two or more samples. The specific structure of the selected intraoperative cultures with the proposed aseptic revisions is shown in Figure 2.

In 8 out of 10 cases, the causative agents were coagulase-negative staphylococci, 6 out of 8 cases were MRSE pathogens. In two cases, anaerobic bacteria (Propionibacterium granulosum and Parvimonas micra) were the causative agents of infection.

Since the laboratory picture is diverse and ambiguous and does not make it possible to reliably judge the presence of infection, we could confirm the infection only on the basis of the results of bacteriological culturing (Table 3).

The growth of the pathogen from the removed components was detected in all 10 patients. The aspirate was not taken in four cases ("dry" joint); in one case out of 6 others, the absence of growth of microorganisms in the punctate was noted in the presence of growth from the removed components of the endoprosthesis.

Table 1

Deviations of laboratory parameters from accepted threshold criteria

Year	Knee joint									Hip joint								
	Parameter									Parameter								
	CRP			D-dimer			ESR			CRP			D-dimer			ESR		
	Measurements, n	Deviations, absolute number	Percentage of deviations	Measurements, n	Deviations, n	Percentage of deviations	Measurements, n	Deviations, n	Percentage of deviations	Measurements, n	Deviations, absolute number	Percentage of deviations	Measurements, n	Deviations, absolute number	Percentage of deviations	Measurements, n	Deviations, n	Percentage of deviations
2017	50	7	14,0	56	22	39,3	60	6	10,0	55	9	16,4	73	22	30,1	76	7	9,2
2018	61	8	13,1	63	27	42,9	65	9	13,8	93	18	19,4	103	43	41,7	109	8	7,3
2019	54	6	11,1	63	20	31,7	63	6	9,5	81	14	17,3	87	45	51,7	87	15	17,2
Total	165	21	12,7	182	69	37,9	188	21	11,2	229	41	17,9	263	110	41,8	272	30	11,0

* ICM, 2018.

Table 2

The number of positive results of microbiological studies of intraoperative biomaterials

Year	Knee	Positive	Hip	Positive	Total
2017	60	0	82	2	142
2018	70	0	114	3	184
2019	65	0	91	6	156
Total	195	0	285	10	480

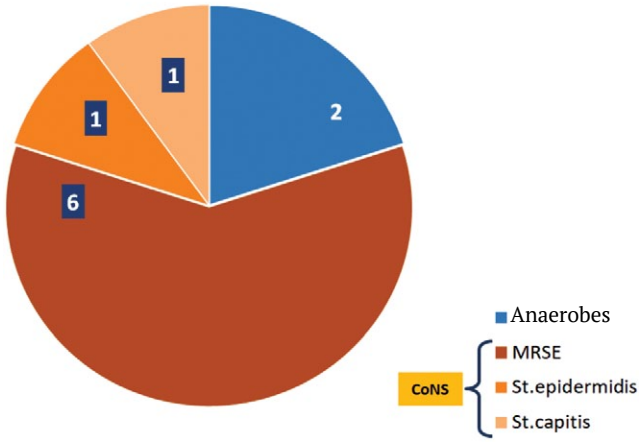


Fig. 2. Species structure of isolated microorganisms (number of results)

Table 3

Results of studies of patients with "unexpected" infections

No of patient	Age, years	The time period from the initial surgery to the present, years	ESR, mm/h	CRP, mg/l	D-dimer, ng/ml	Cytosis № 1 Cells in 1 µl	Cytosis № 2 Cells in 1 µl	Cytosis № 3 Cells in 1 µl	Intraoperative cytosis, PMN%	Number of positive samples (number of samples taken)
1	64	5,6	17	8,4	834	No**	No **	413	Not taken	6 (8)
2	63	13	36	22,4	278	No **	No **	980	35*	4 (8)
3	39	0,5	19	5,5	1060	15*	11	10*	80*	2 (5)
4	65	3,75	30	16,7	2250	No **	No **	0	2500 (88)	5 (7)
5	61	3,75	18	16	1258	20*	0	11	Not taken	5 (7)
6	58	0,75	17	8,4	812	No **	Нет**	80*	1400 (72)	4 (7)
7	45	6,08	21	7,2	1293	No **	Нет**	1100	Not taken	5 (5)
8	50	0,75	25	9,7	955	No **	30	22*	7250 (95)	6 (7)
9	42	5,0	13	9,4	843	Not taken	25	710	Not taken	6 (7)
10	59	3,83	28	12,7	1039	50*	650*	525*	13750 (97)	4 (5)

* - hemorrhagic nature of the punctate; ** - synovial fluid analysis was performed at the place of residence.

In 9 out of 10 patients, the infection was detected after the primary arthroplasty, in one — after the revision arthroplasty. In all cases, the infection was regarded as late chronic (the earliest occurred 6 months after the arthroplasty). In one patient, both markers of PJI were elevated; in 6 cases, both indicators (CRP and ESR) were below the threshold values. Isolated increase in CRP was noted in 4 cases. The reason for the revision in 8 out of 10 cases was the aseptic loosening of the endoprosthesis components. In 2 cases, there was a mechanical cause of the revision — migration of the acetabulum component with protrusion into the pelvis — and a periprosthetic fracture consolidated by the time of surgery.

All patients were prescribed systemic antibacterial therapy: intravenously during inpatient treatment and then, after discharge, orally for 10—12 weeks. The replacement of the drug, taking into account the sensitivity of the microorganism in the early postoperative period, was carried out on the 2nd-6th day after the surgery, as the result of microbiological examination was obtained.

Since an aseptic revision was supposed, only unstable components of hip joint were replaced in some patients (in 3 patients — the acetabulum component, in one — the femoral component), in other cases both components were replaced.

At the stage of catamnesis, following the results of an active telephone call of patients with positive culture, one of 10 patients had a problem in the joint: 7 months after the surgery, periodic pain appeared in the joint, after another 10 months (after the COVID-19), the pain intensified, the temperature began to rise periodically, which, based on the patient's complaints, can presumably be regarded as PJI. Revision was not carried out due to the patient's failure to appear for hospitalization. Two patients noted periodic joint pain during weather changes or after prolonged activity, the remaining 7 patients did not make any special complaints. All patients noted a decrease in pain syndrome in the postoperative period compared to the result of the previous surgery, and were satisfied with the surgery.

In 470 patients with negative culture, 63% of patients showed up for a follow–up examination a year after the revision, including four patients with typical PJI complaints: two with Knee joint endoprosthesis (5 months and 2 years 10 months after the previous surgery), two with hip joint endoprosthesis (a year and 3 years, respectively). In each of them, the infection was confirmed clinically and laboratory at the preoperative and intraoperative stages. Four patients, which accounted for 1.4% of those who showed up for a control examination, underwent a two-stage revision arthroplasty.

Discussion

Despite all diagnostic efforts, in many patients, the PJI remains unrecognized until the moment of revision [21]. According to the classification of D.T. Tsukayama et al., unexpected infection — "positive intraoperative culture" — belongs to the fourth type of the surgery area deep infection [30].

The most common complaint in these patients is joint pain, while there is no consensus on the systematic screening of infection with aseptic revision joint replacement. According to number of authors, each case with pain syndrome in the area of THA, especially during the first 2–3 years after surgery, should be considered as a potential infectious complication, up to evidence to the contrary [12, 31].

The study showed that in preparation for aseptic revision and their performing, some of the PJI that were not detected by available methods remained out of sight. In the presence of mechanical complications, surgeons ignored performing diagnostic joints punctures, since the cause of the complication and the reason for the revision were not in doubt. The successful results of preoperative studies also testified in favor of the absence of an infectious process. Meanwhile, we have identified a certain part of the "unexpected" infections associated with mechanical complications.

In our opinion, in order to exclude PJI in any revision, there are indications for the study of serum markers of inflammation and the analysis of aspirate from the joint cavity. In PJI caused by highly virulent pathogens, inflammatory markers such as ESR and CRP are usually elevated; in the case of chronic (low-symptom) infection, changes in these indicators are less common, and their level has secondary importance [12, 32].

It is known that normal blood counts do not exclude the presence of infection (which was the case in our study), and deviations in their level are nonspecific for PJI and may be manifestations of an infectious process of any localization or other concomitant pathological process. With a simultaneous increase in the level of ESR and CRP, the combined sensitivity of the latter increases to 96%, but the specificity remains low [23]. If both indicators are negative, then this corresponds to a high negative prognostic value, but does not completely exclude infection [12, 33]. In our study, CRP was above the threshold values in 11.1–19.4% of all cases; among "unexpected" infections — in 6 out of 10 cases it was below the threshold values with confirmed PJI.

Despite the fact that the Second ICM included the D-dimer as a secondary criterion ("small" marker) for PJI, its diagnostic role deserves further study. For the diagnosis of PJI, the D-dimer level has the same or less significant importance than CRP and ESR. According to colleagues, the frequency of false positive results

may be 46%, the frequency of false negative results — 17%; at the same time, sensitivity and specificity may remain relatively high. Causes contributing to an increase in D-dimer values in patients with aseptic loosening: thrombotic disorders, inflammatory diseases, postoperative conditions, oncological diseases, infections, injuries, hemorrhages and even coronavirus disease (COVID-19). The D-dimer is mainly a marker of systemic fibrinolysis and fibrin turnover, so its values can potentially be influenced by many factors: age, gender, body mass index, concomitant cardiovascular diseases requiring treatment with anticoagulants [34]. The high proportion of D-dimer values deviations from the norm in our study (41.8%) can be explained by the lack of information about concomitant diseases of patients that could have a significant impact on D-dimer values.

Preoperative aspiration of synovial fluid as an invasive procedure is not mandatory for the study, it is usually performed in patients with suspected PJI, which corresponds to the routine clinical practice in some medical organizations. Bacteriological examination makes it possible to determine the antibacterial sensitivity of the microorganism, which is of extremely high value for determining the tactics of further treatment [21]. With the standard approach, the examination of the punctate in the preoperative period is not always carried out in most medical organizations [8, 21]. We assume that the aspirate analysis should be performed in all patients regardless of the level of serum markers of inflammation.

When puncturing the cavity around the prosthesis, it is not always possible to isolate the causative agent of PJI. It is known that many microorganisms that cause PJI are capable of forming biofilms, which sometimes does not allow isolating the infecting agent by traditional cultural methods [12, 35]. If there is suspicion of PJI, and the aspirate study gave a negative result, for example, with Punctio sicca, an open diagnostic biopsy can be used — a more reliable method compared to the aspirate study both in sensitivity (82% vs. 64%) and specificity (98% vs. 96%) [36]. If PJI is suspected, the need for an additional invasive procedure should always be assessed.

With a wide coverage of patients with punctures before aseptic revision, it is not always possible to obtain a sufficient amount of punctate for examination, which is characteristic of the aseptic process. With the existing different approaches of ICM and EBJIS to the collection of synovial fluid, in our case, 13.9% of the studies were possible only by diluting the punctate with saline solution (according to EBJIS). If possible, the punctate should not contain blood inclusions, because this can mimic leukocytosis [37, 38]. In our case, more than 30% of the received punctures were hemorrhagic.

With significant dilution of synovial fluid with saline solution, significant dilution of cell mass can distort the results of laboratory studies; it is recommended to exclude these low-quality samples from future diagnostic studies, since an artificial decrease in the sensitivity of the test will be observed [23, 38]. On the contrary, hemorrhagic impurities can simulate false leukocytosis. Nevertheless, we used dilute and hemorrhagic samples for diagnosis as accessory with appropriate comments for clinicians to maintain infectious alertness.

The study of the punctate gives us two diagnostic criteria at once to help us: bacteriological culture and analysis of aspirate with cell differentiation. In our study, preoperative examination of synovial fluid showed the absence of pathogens growth and cytosis during a three-time preoperative examination of the joint punctate, which in 97.9% of cases coincided with negative results of the intraoperative materials study, which indicates the high efficiency of the proposed examination algorithm. However, it should be keep in mind that it is not necessary to rely entirely on the result of cytosis, since the accepted cytosis thresholds are unacceptable for hemorrhagic samples for 6 weeks from the day of surgery, as well as for systemic diseases, dislocation and fracture [18].

According to G.A. Kukovenko et al., three-time examination makes it possible to correctly diagnose and isolate the causative agent of deep PJI [39]. Our analysis of the punctate microbiological examination results showed that with an increase in their multiplicity, the number of positive results increases. This conclusion is confirmed by the fact that during the third puncture in patients with septic process, the growth of microorganisms was detected in another 6.7% of cases. If a three-time study had not been conducted, then this part of the cases would have been recognized as aseptic and would subsequently have been qualified as septic already during the revision and in the postoperative period.

For clinicians, preoperative data has great importance in choosing surgical tactics — in our case, they did not cause suspicion. At the same time, cytosis detected intraoperatively in three patients (>2000 cells / μl) in combination with other complications (mechanical, somatic) did not contribute to infectious alertness, and this could affect the change in the course (staging) of the surgery. We identified "unexpected" infections only in the postoperative period, after bacteriological examination of intraoperative materials.

According to the literature, the prevalence of "unexpected" positive intraoperative culture ranges from 4% to 38%, which may be due to differences in preoperative diagnosis, features of the cases selection of aseptic revisions, the number of culture samples taken, as well as be associated with possible contami-

nation of biomaterial, insufficient sample size [8]. The average prevalence of "unexpected" infection among the patients included in this review was 10.5% [8]. The gap between our result (2.08%) and the literature data may be due to the short follow-up period of patients in this study (3 years), as well as different approaches to the frequency of preoperative and intraoperative joint punctures in non-infectious complications after arthroplasty.

Some of authors consider "unexpected" infections mainly in the context of aseptic loosening of components. In our study, the proportion of "unexpected" infections in the structure of aseptic loosening was only 3.75% compared to 10.0% in G. Renard et al [19].

According to the literature data, "unexpected" infections are almost twice as often detected in hip joint than in knee joint [8]. All the cases we identified concerned THA, which is explained, as we believe, by the difficulty of obtaining synovial fluid from hip joint.

In the studies of colleagues, it is noted that the most common microorganisms in "unexpected" infections are coagulase-negative staphylococci, in second place is Propionibacterium; virulent organisms such as Staphylococcus aureus and enterococci are less common [14]. Our results confirm these conclusions: methicillin-resistant Staphylococcus epidermidis — MRSE was the leader in the microbial landscape.

The use of molecular biological methods such as polymerase chain reaction (PCR) for the diagnosis of PJI has been well studied [8, 12, 40, 41, 423] and it would contribute, on the one hand, to the additional detection of microorganisms. On the other hand, these methods are very sensitive to contamination [21]. In addition, most of them as test kits are not available to many medical organizations and therefore are still far from routine use in everyday clinical practice.

Measurement of alpha-defensin in synovial fluid is used as a supplement to existing tests for the diagnosis of PJI as the most specific preoperative test [14, 18]. Its use also has its limitations — false positive results are possible in cases of hemorrhagic or dilute sample, with metallosis. This test is used in daily clinical practice in our Center to a limited extent in doubtful cases due to its high cost.

The tactics of further revision depends on the verification of the etiological factor of the complication that led to the aseptic revision — whether it should be carried out by a one-stage method or in two stages. When there is no data for the infectious process before surgery, and pathogens difficult to eradicate are isolated from intraoperative material, for which the choice of active antimicrobials is limited, one-stage replacement of the endoprosthesis can lead to subsequent relapses and repeated revisions.

Currently, one-stage revision arthroplasty is used only to a limited extent in the treatment of PJI, despite the obvious economic benefits in comparison with two-stage revisions. Both approaches have their pros and cons.

There is an opinion that one-stage revision in patients with PJI reduces total intraoperative blood loss, negative impact on concomitant diseases and the mortality rate of patients, not inferior to the results of two-stage treatment in terms of infection suppression [41]. It is fundamentally important to completely remove all the components of the endoprosthesis and remaining bone cement if it presents [12]. The absolute advantage of this surgery is the simultaneous relief of infection and the rapid restoration of lost limb function, as well as a single course of antibiotic therapy [41].

However, compared with two-stage revisions, one-stage has a number of limitations of use in conditions of polymicrobial infection, immunosuppression, significant defects in the bone and soft tissues of the affected joint [43]. At the same time, it is believed that two-stage revision in chronic (low-symptomatic) PJI has a high success rate compared to a one-stage revision: the risk of reinfection is 33.9% higher than with a two-stage revision [12].

The tactics of joint punctures practiced in the Center in the preoperative period with any upcoming revision allows you to immediately differentiate obvious PJI. Our additional studies make it possible to detect "unexpected" infections at the level of 2.08% of all aseptic revisions, which is significantly less than the data of the world literature — 4–38% [8].

Timely chosen treatment tactics in the identified cases (the appointment of antibacterial therapy in the postoperative period after one-stage revisions and at the outpatient stage, taking into account the sensitivity of the isolated microorganism) allowed to achieve a good treatment result in 9 out of 10 patients.

Valuable information for diagnosis was added by the examination of the aspirate from the joint. The analysis of the studied publications showed that foreign colleagues did not perform triple punctures en masse, which explains the higher rate of detection of "unexpected" infections during aseptic revisions in the postoperative period. The tactic of three-time punctate studies used by us logically increases the proportion of detected infection in the preoperative period, which allows us to attribute these cases to PJI and apply appropriate surgical treatment tactics to them. We assume that this is the reason for the differences in the frequency of detection of "unexpected" PJI in our study and in the literature.

The maximum coverage of patients with joint punctures (from one to three) before aseptic revisions, and especially during their implementation with mandatory cytological and microbiological studies of the punctate, allowed us to choose the optimal

stage of surgical treatment of patients and reduce the risk of relapses.

According to our data, 9 out of 10 patients with "unexpected" infections in the medium term (more than one year) had a favorable outcome of surgical treatment.

Study limitations

The results of the study could be affected by incomplete data of laboratory and bacteriological studies in some patients at the pre- and intraoperative stages (lack of research results, non-compliance with the frequency of their conduct), non-attendance of some patients for a follow-up examination. It should be noted that we included low-quality punctates (synovial fluid) in the data processing, which is also a limitation of the study, since it indicates that in 43.9% of cases it is not possible to obtain biological material that meets the requirements for cytological examination. This significantly reduces the diagnostic capabilities of cytological examination of the punctate. The program of our research differs from the methodological approaches of other authors, which requires an additional multicenter or meta-study on this problem according to a single protocol.

Conclusions

The detection of infection where it was not supposed to be and its identification make it possible to prescribe a rational course of antibacterial therapy after one-stage revisions. Successful results of treatment of patients with "unexpected" infections in 90% of cases make it possible to use this approach in planning of revision interventions. The experience gained allows us to use one-stage revision in certain cases in the treatment of PJI.

Ethical expertise

The study was carried out in accordance with the ethical principles of the Helsinki Declaration (World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects, 2013), "Rules of Clinical Practice in the Russian Federation" (Order of the Ministry of Health of Russia dated 06/19/2003 No. 266).

Informed consent

The patients gave written informed consent to participate in the study and publish its results.

References

1. Shubnyakov I.I., Tikhilov R.M., Denisov A.O., Akhmedilov M.A., Cherny A.Z., Totoev Z.A. et al. [What Has Changed in the Structure of Revision Hip Arthroplasty?]. *Travmatologiya i Ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2019;25(4):9-27. (In Russian). doi: 10.21823/2311-2905-2019-25-4-9-27.
2. Nikolaev N.S., Malyuchenko L.I., Preobrazhenskaya E.V., Karpukhin A.S., Yakovlev V.V., Maksimov A.L. [The use of individual components of the acetabulum in hip arthroplasty in posttraumatic coxarthrosis]. *Genij Ortopedii*. 2019;25(2):207-213. (In Russian). doi: 10.18019/1028-4427-2019-25-2-207-213.
3. Fevang B.T., Lie S.A., Havelin L.I., Engesaeter L.B., Furnes O. Improved results of primary total hip replacement. *Acta Orthop*. 2010;81(6):649-659. doi: 10.3109/17453674.2010.537807.
4. Kowalik T.D., DeHart M., Gehling H., Gehling P., Schabel K., Duwelius P., Mirza A. The Epidemiology of Primary and Revision Total Hip Arthroplasty in Teaching and Nonteaching Hospitals in the United States. *J Am Acad Orthop Surg*. 2016;24(6):393-398. doi: 10.5435/JAAOS-D-15-00596.
5. Patel A, Pavlou G, Mújica-Mota RE, Toms AD. The epidemiology of revision total knee and hip arthroplasty in England and Wales: a comparative analysis with projections for the United States. A study using the National Joint Registry dataset. *Bone Joint J*. 2015;97-B(8):1076-1081. doi: 10.1302/0301-620X.97B8.35170.
6. Bardou-Jacquet J., Souillac V., Mouton A., Chauveaux D. Primary aseptic revision of the femoral component of a cemented total hip arthroplasty using a cemented technique without bone graft. *Orthop Traumatol Surg Res*. 2009;95(4):243-248. doi: 10.1016/j.otsr.2009.04.007.
7. Roberts V.I., Esler C.N., Harper W.M. A 15-year follow-up study of 4606 primary total knee replacements. *J Bone Joint Surg Br*. 2007;89(11):1452-1456. doi: 10.1302/0301-620X.89B11.19783.
8. Purudappa P.P., Sharma O.P., Priyavadana S., Sambandam S., Villafuerte J.A. Unexpected positive intraoperative cultures (UPIC) in revision Hip and knee arthroplasty- A review of the literature. *J Orthop*. 2019;17:1-6. doi: 10.1016/j.jor.2019.06.028.
9. Labek G., Thaler M., Janda W., Agreiter M., Stöckl B. Revision rates after total joint replacement: cumulative results from worldwide joint register datasets. *J Bone Joint Surg Br*. 2011;93(3):293-297. doi: 10.1302/0301-620X.93B3.25467.
10. Prokhorenko V.M., Azizov M.Zh., Shakirov Kh.Kh. [Revision hip arthroplasty: a case-control study]. *Sovremennye problemy nauki i obrazovaniya* [Modern problems of science and education]. 2016;6; Available from: http://www.science-education.ru/ru/article/view?id=25677. (In Russian).
11. Postler A., Lützner C., Beyer F., Tille E., Lützner J. Analysis of Total Knee Arthroplasty revision causes. *BMC Musculoskelet Disord*. 2018;19(1):55. doi: 10.1186/s12891-018-1977-y.

12. Winkler T., Trampuz A., Renz N., Perka C., Bozhkova S.A. [Classification and algorithm for diagnosis and treatment of hip prothetic joint infection]. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2016;(1):33-45. (In Russian). doi: 10.21823/2311-2905-2016-0-1-33-45.
13. Sereda A.P., Kavalersky G.M., Murylev V.Yu., Rukin Ya.A. [Periprosthetic infection diagnosis. Part 1: serology]. *Travmatologiya i ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2014;(4):115-126. (In Russian). doi: 10.21823/2311-2905-2014-0-4-4-14.
14. Anagnostakos K., Thiery A., Meyer C., Sahan I. Positive Microbiological Findings at the Site of Presumed Aseptic Revision Arthroplasty Surgery of the Hip and Knee Joint: Is a Surgical Revision Always Necessary? *Biomed Res Int.* 2020;2020:2162136. doi: 10.1155/2020/2162136.
15. Kapadia B.H., Berg R.A., Daley J.A., Fritz J., Bhave A., Mont M.A. Periprosthetic joint infection. *Lancet.* 2016;387(10016):386-394. doi: 10.1016/S0140-6736(14)61798-0.
16. Parvizi J., Fassihi S.C., Enayatollahi M.A. Diagnosis of Periprosthetic Joint Infection Following Hip and Knee Arthroplasty. *Orthop Clin North Am.* 2016;47(3):505-515. doi: 10.1016/j.ocl.2016.03.001.
17. Parvizi J., Tan T.L., Goswami K., Higuera C., Della Valle C., Chen A.F., Shohat N. The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria. *J Arthroplasty.* 2018;33(5):1309-1314.e2. doi: 10.1016/j.arth.2018.02.078.
18. 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(9):742-750. doi: 10.2106/JBJS.17.01005.
19. Renard G., Laffosse J.M., Tibbo M., Lucena T., Cavaignac E., Rouvillain J.L. et al. Periprosthetic joint infection in aseptic total hip arthroplasty revision. *Int Orthop.* 2020;44(4):735-741. doi: 10.1007/s00264-019-04366-2.
20. Shpinyak S.P., Babushkina I.V., Maksyushina T.D., Galashina E.A., Chibrikova Yu.A., Bondarenko A.S., Norkin I.A. [The methods of deep periprosthetic infection diagnostics in the area of knee joint (Review)]. *Saratovskij nauchno-medicinskij zhurnal* [Saratov Journal of Medical Scientific Research]. 2018;14(3):607-610. (In Russian).
21. Moojen D.J., van Hellemondt G., Vogely H.C., Burger B.J., Walenkamp G.H., Tulp N.J. et al. Incidence of low-grade infection in aseptic loosening of total hip arthroplasty. *Acta Orthop.* 2010;81(6):667-673. doi: 10.3109/17453674.2010.525201.
22. Ribera A., Morata L., Moranas J., Agulló J.L., Martínez J.C., López Y. et al. Clinical and microbiological findings in prosthetic joint replacement due to aseptic loosening. *J Infect.* 2014;69(3):235-243. doi: 10.1016/j.jinf.2014.05.003.
23. Figueiredo A., Ferreira R., Alegre C., Judas F., Fonseca F. Diagnosis of Periprosthetic Joint infection: from Novel Synovial Fluid Biomarkers to Identification of the Etiological Agent. *Nov Tech Arthritis Bone Res.* 2018;2(4):555594. doi: 10.19080/ NTAB.2018.02.555595.
24. Zahar A., Webb J., Gehrke T., Kendoff D. One-stage exchange for prosthetic joint infection of the hip. *Hip Int.* 2015;25(4):301-307. doi: 10.5301/hipint.5000264.
25. Zeller V., Lhotellier L., Marmor S., Leclerc Ph., Krain A., Graff W. et al. One-stage exchange arthroplasty for chronic periprosthetic hip infection: results of a large prospective cohort study. *J Bone Joint Surg Am.* 2014;96(1):e1. doi: 10.2106/JBJS.L.01451.
26. Anagnostakos K., Fink B. Antibiotic-loaded cement spacers — lessons learned from the past 20 years. *Expert Rev Med Devices.*2018;15(3):231-245. doi: 10.1080/17434440.2018.1435270.
27. Janz V., Bartek B., Wassilew G.I., Stuhlert M., Perka C.F., Winkler T. Validation of Synovial Aspiration in Girdlestone Hips for Detection of Infection Persistence in Patients Undergoing 2-Stage Revision Total Hip Arthroplasty. *J Arthroplasty.* 2016;31(3):684-687. doi: 10.1016/j.arth.2015.09.053.
28. Nikolaev N.S., Lyubimova L.V., Pchelova N.N., Preobrazhenskaya E.V., Alekseeva A.V. [Treatment of Periprosthetic Infection with Silver-Doped Implants Based on Two-Dimensionally Ordered Linear Chain Carbon]. *Travmatologiya i Ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2019;25(4):98-108. doi: 10.21823/2311-2905-2019-25-4-98-108. (In Russian).
29. Parvizi J., Tan T.L., Goswami K., Higuera C., Della Valle C., Chen A.F. et al. The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence-Based and Validated Criteria. *J Arthroplasty.* 2018;33(5):1309-1314.e2. doi: 10.1016/j.arth.2018.02.078.
30. Tsukayama D.T., Estrada R., Gustilo R.B. Infection after total hip arthroplasty. A study of the treatment of one hundred and six infections. *J Bone Joint Surg Am.* 1996;78(4):512-523. doi: 10.2106/00004623-199604000-00005.
31. Zimmerli W. Infection and musculoskeletal conditions: Prosthetic-joint-associated infections. *Best Pract Res Clin Rheumatol.* 2006;20(6):1045-1063. doi: 10.1016/j.berh.2006.08.003.
32. Corvec S., Portillo M.E., Pasticci B.M., Borens O., Trampuz A. Epidemiology and new developments in the diagnosis of prosthetic joint infection. *Int J Artif Organs.* 2012;35(10):923-934. doi: 10.5301/ijao.5000168.
33. Trampuz A., Perka C., Borens O. Gelenkprothesen infektion: Neue Entwicklungen in der Diagnostik und Therapie [Prosthetic joint infection: new developments in diagnosis and treatment]. *Dtsch Med Wochenschr.* 2013;138(31-32):1571-1573. doi: 10.1055/s-0033-1343280. (In German).
34. Balato G., De Franco C., Balboni F., De Matteo V., Ascione T., Baldini A. et al. The role of D-dimer in periprosthetic joint infection: a systematic review and meta-analysis. *Diagnosis (Berl).* 2021. doi: 10.1515/dx-2021-0032. Online ahead of print.
35. Frommelt L. Gelenkpunktat und Erregernachweis bei periprothetischer Infektion [Aspiration of joint fluid for detection of the pathogen in periprosthetic infection]. *Orthopade.* 2008;37(10):1027-1034. doi: 10.1007/s00132-008-1345-y. (In German).

36. Fink B., Gebhard A., Fuerst M., Berger I., Schäfer P. High diagnostic value of synovial biopsy in periprosthetic joint infection of the hip. *Clin Orthop Relat Res.* 2013;471(3):956-964. doi: 10.1007/s11999-012-2474-5.
37. Ghanem E., Houssock C., Pulido L., Han S., Jaberi F.M., Parvizi J. Determining «true» leukocytosis in bloody joint aspiration. *J Arthroplasty.* 2008;23(2):182-187. doi: 10.1016/j.arth.2007.08.016.
38. Deirmengian C., Feeley S., Kazarian G.S., Kardos K. Synovial Fluid Aspirates Diluted with Saline or Blood Reduce the Sensitivity of Traditional and Contemporary Synovial Fluid Biomarkers. *Clin Orthop Relat Res.* 2020 Aug;478(8):1805-1813. doi: 10.1097/CORR.0000000000001188.
39. Kukovenko G.A., Elizarov P.M., Alekseev S.S., Sorokina G.L., Ivanenko L.R., Erokhin N.E. et al. Importance of the Algorithm for Diagnosis of Late Deep Periprosthetic Hip Infection. *Travmatologiya i Ortopediya Rossii* [Traumatology and Orthopedics of Russia]. 2019;25(4):75-87. doi: 10.21823/2311-2905-2019-25-4-75-87. (In Russian).
40. Kobayashi N., Procop G.W., Krebs V., Kobayashi H., Bauer T.W. Molecular identification of bacteria from aseptically loose implants. *Clin Orthop Relat Res.* 2008;466(7):1716-1725. doi: 10.1007/s11999-008-0263-y.
41. Ermakov A.M., Klyushin N.M., Ababkov Yu.V., Tryapichnikov A.S., Koyushkov A.N. [One-stage revision arthroplasty in the treatment of periprosthetic hip joint infection]. *Genij Ortopedii.* 2019;25(2):172-179. doi: 10.18019/1028-4427-2019-25-2-172-179. (In Russian).
42. Dobrovol'skaya N.Yu., Prishchepa N.P., Preobrazhenskaya E.V., Pchelova N.N. [PCR research as an auxiliary method for diagnostics of periphresitical infection after endostreditision of joints (clinical case)]. *Klinicheskaya laboratornaya diagnostika* [Clinical Laboratory Diagnostics]. 2020;65(5):332-336. doi: 10.18821/0869-2084-2020-65-5-332-336. (In Russian).
43. Ilchmann T., Zimmerli W., Ochsner P.E., Kessler B., Zwicky L., Graber P. et al. One-stage revision of infected hip arthroplasty: outcome of 39 consecutive hips. *Int Orthop*. 2016;40(5):913-918. doi: 10.1007/s00264-015-2833-4.

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All authors have read and approved the final version of the manuscript of the article. All authors agree to bear responsibility for all aspects of the study to ensure proper consideration and resolution of all possible issues related to the correctness and reliability of any part of the work.

Conflict of interest:
The authors declare that there is no conflict of interest.