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Possibilities of latent PJI detection in revision knee arthroplasty

A.N. Panteleev✉, S.A. Bozhkova, P.M. Preobrazhensky, A.V. Kazemirsky

Vreden National Medical Research Center of Traumatology and Orthopedics, Saint Petersburg, Russian Federation

Corresponding author: Alexander N. Panteleev, alex.pant95@mail.ru

Abstract

Introduction The paper presents a comparative analysis of routine screening methods and the EBJIS 2021 algorithm in detection of latent periprosthetic joint infection in patients admitted for revision knee arthroplasty due to aseptic loosening and after spacer implantation. **Materials and methods** Group 1 included 49 patients who underwent revision knee arthroplasty due to aseptic loosening, group 2 were 47 patients with PJI after spacer implantation. **Results and discussion** There were no significant differences between patient groups in terms of age, gender, and preoperative ESR and CRP levels. In 62.2 % of all cases, the aspirate was inappropriate for cytological examination; this fact limited its diagnostic value. The most frequently intraoperatively isolated pathogen in both groups was coagulase-negative staphylococci. However, in 70 % of cases these results were not diagnostically significant, and infection was diagnosed only in 8.2 % of cases in group 1 and 12.8 % in group 2. Moreover, the chances of isolating the pathogen from tissue biopsies were 5.6 times higher than from intraoperative aspirate (OR = 5.6, 95 % CI = 1.2-26.4). In case of negative preoperative aspirate, in almost 25 % of cases, pathogens were isolated from intraoperative tissues, 40.9 % of them were diagnostically significant. The chances of its detection increased 4.7 times in combined increase in ESR and CRP blood level (OR = 4.686, 95 % CI = 0.765-28.700). Using EBJIS 2021 criteria, infection was confirmed in more than 10 % of cases in each group, and the diagnostic significance of the criteria exceeded the significance of using routine screening methods. At a follow-up period of more than 2 years, the effectiveness of treatment was 95.3 %, while signs of infection were detected in 4.7 % of cases, regardless of the group. **Conclusion** EBJIS 2021 criteria are characterized by high diagnostic sensitivity and specificity and enable to identify periprosthetic joint infection in knee revision cases even in its latent form and to correct treatment tactics in patients without a history of PJI.

Keywords: revision arthroplasty, knee joint, periprosthetic joint infection

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INTRODUCTION

Periprosthetic joint infection (PJI) still remains a serious medical and social problem. According to the registry of the Vderen NMRC for TO, PJI is the main reason for revision arthroplasty, accounting for more than 50 % annually [1]. In the structure of the causes of revision surgeries after primary arthroplasty (PA), according to the National Arthroplasty Registry of the Australian Orthopedic Association, in 2019 PJI was 23.7 %, ranking second after aseptic instability (24.7 %) [2]. It is assumed that the projected increase in the number of primary athroplasty by 43 % would lead to an even greater increase in the number of annual revision operations by 90 % in 2050 [3].

The course of PJI is characterized by pronounced clinical manifestations in acute infection caused by highly virulent pathogens, and it may be asymptomatic, for example, in latent PJI caused by low-virulent pathogens. The latent course of PJI is suspected in cases where there are no local manifestations of an acute inflammatory process and possible explanations for pain, edema and/or a decrease in the range of motion in the operated joint are absent [4]. The latent PJI presents significant difficulties for diagnosis, while an error in the differential diagnosis of PJI and other causes of revision arthropasty (RA) leads to unfavorable clinical consequences and significantly increases the financial costs of further treatment [5, 6]. The currently available screening tests and their combinations are not able to provide convincing data on the presence or absence of latent PIP in a number of cases, which requires improving the algorithms for the timely detection of a newly developed or recurrent infectious process before performing revision arthroplasty. The most modern diagnostic algorithm currently available is the one proposed in 2021 by the European Society for Infection of Bones and Joints (EBJIS) with the support of the Society for Musculoskeletal Infection (MSIS) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) [7]. According to the authors, the three-level concept of identifying PJI should allow for more effective detection of PJI cases that would traditionally not be classified as infectious using the previously proposed EBJIS or MSIS criteria, but this requires further research.

Purpose To study the diagnostic significance of routine screening methods (combined elevation of ESR and CRP, microbiological and cytological study of the aspirate) and the EBJIS 2021 algorithm in identifying latent PJI in patients admitted for revision knee arthroplasty due to aseptic instability of the implant components and after implantation of a spacer.

MATERIAL AND METHODS

Patients

The study was retrospective. We analyzed the records of 127 patients admitted for knee joint (KJ) revision arthroplasty to the clinic of the Vreden center in the period 2018–2019.

To achieve homogeneity of the comparison groups, the criteria for inclusion into the study were formulated:

– history of primary TKA in the absence of a documented infection in the KJ area before the primary intervention or sanitizing surgery with the removal of the implant components and the installation of an antimicrobial spacer due to PJI;

– no growth of microorganisms in the preoperative aspirate or unavailable aspirate;

– available results of microbiological tests of periprosthetic tissues.

As a result, 96 patients were included into the study who were divided into comparison groups depending on the RA cause: group 1 were 49 patients who underwent RA due to aseptic instability of the implant components, group 2 were 47 patients with a spacer previously implanted for PJI (Fig. 1). The median follow-up was 27 months (range, 18–36 months).

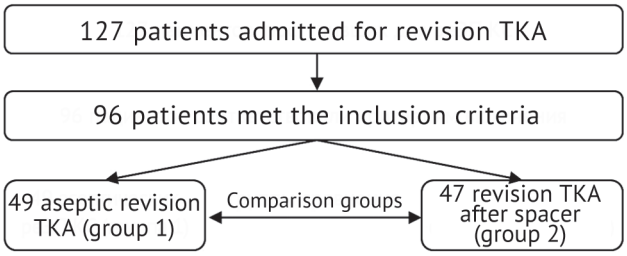

Fig. 1 Study design diagram

Methods of study

According to medical records, all patients included into the study were studied for:

– ESR and CRP levels at the time of hospitalization;

– results of cytological (CI) and microbiological (MBI) investigations of preoperative aspirate;

– results of the MBI of intraoperative biomaterial and the structure of the isolated pathogens;

– follow-up outcomes of revision TKA (absence of clinical and laboratory signs of PJI recurrence at the time of follow-up or questionnaire of patients was taken as a positive outcome; the need to perform repeated surgical interventions after TKA due to PJI was regarded as a poor outcome).

An assessment was made of the diagnostic significance of the results of screening laboratory blood parameters (CRP and ESR) and CI of the joint fluid (cytosis and the proportion of PMN), as well as a comprehensive assessment according to the EBJIS 2021 criteria (Table 1) in comparison with the results of MBI of the intraoperative material. According to the EBJIS criteria, three groups of patients are distinguished: infection unlikely, infection likely and infection confirmed.

According to medical records, all patients underwent clinical and laboratory tests at the preoperative stage, including diagnostic aspiration of the knee joint. The aspirate material was sent for MBI; in the absence of blood impurities in the aspirate, additional CI was performed. The MBI results were taken as diagnostically significant (DS) in cases of isolating a strain of a pathogenic microorganism from one sample or identical strains of one opportunistic pathogen from ≥ 2 samples of biomaterials.

Table 1

Diagnostic criteria for PJI, EBJIS 2021 adapted for Russian

Criteria	PJI unlikely	Infection likely (2 positive and more «+» criteria, one of which is main)	PJI confirmed (any positive «+» criteria)
Main criteria			
Clinical features	Clear alternative reason of joint dysfunction confirmed	1) Rg-signs of loosening within the first 5 years after implantation 2) Previous wound healing problems 3)history of recent fever or bacteraemia 4) Purulence around the prosthesis	Sinus tract with evidence of communication to the joint or prosthesis
CRP		> 10 mg/l	
Synovial fluid cytological analysis			
Leukocyte count (cells/ml)	≤ 1.500	> 1.00	> 3.000
PMN (%)	≤ 65 %	> 65 %	> 80 %
Synovial fluid biomarkers			
Alpha-defensin			«+»
Microbiology			
Aspiration fluid		Positive culture	
Intraoperative fluid and tissue	All cultures negative	Single positive culture	Two positive samples with the same microorganism ≥ 2
Sonication	No growth	> 1 CFU/ml of any organism	> 50 CFU/ml of any organism
Hystology			
High-power field 400x	–	≥ 5 PMN in 1 field	≥ 5 PMN in ≥ 5 fields
Other			
Nuclear imaging	– scintigraphy	+ scintigraphy	

Notes: PJI – periprosthetic infection; Rg – radiological, TKA – knee arthroplasty; CRP – C-reative protein; PMN – polymorphonuclear neutrophils, MO – microorganisms

Surgical technique

All patients included into the study underwent revision TKA with removal of implant components or with a spacer, cement mantle, if any, debridement of bone and surrounding soft tissues, and abundant lavage of the joint cavity with isotonic sodium chloride solution in group 1 or Lavasept solution in group 2 (not less than 5 liters). The components of the revision implant were fixed using antibiotic-containing bone cement (Refobacin bone cement or DePuy CMW 3 bone cement). The removed components or a spacer were sent to a microbiological laboratory for ultrasound processing and subsequent bacteriological study of the sonic fluid. Five tissue biopsy specimens and synovial fluid, if available, were taken intraoperatively for MBI.

Postoperative care

In the postoperative period, all patients underwent prophylaxis of venous thromboembolic complications. Group 1 patients underwent a course of antibiotic prophylaxis (ABP) according to the approved local protocol (cefazolin, cefuroxime) for up to 3 days. Patients in group 2 received a course of parenteral antibiotic therapy (ABT), agreed with a clinical pharmacologist in accordance with the causative agents of PJI identified at the stage of debridement, for 7–10 days, followed by a switch to oral antibacterial drugs for 1–2 months. After the final MBI results of the intraoperative biomaterial, if necessary, the antibiotic therapy was corrected.

Statistical analysis

The clinical results obtained in the course of the work were analyzed using the STATISTICA 10 software system. Comparison of frequency characteristics (gender, diagnosis in accordance with EBJIS criteria and outcome) of qualitative indicators was carried out using nonparametric methods χ^2, χ^2 Pearson, Fisher's test. Comparison of quantitative parameters (age, levels of inflammation markers and the structure of PJI pathogens) in the study groups was carried out using the Mann-Whitney test and odds ratio (OR). The median (Me) was used as the central characteristic, and the lower (Q1) and upper (Q3) quartiles (25–75 % MCI) were used as the scattering measures. Differences between groups were considered statistically significant at $p < 0.05$.

RESULTS

In our study, the groups were comparable in age and gender representation: the median age in group 1 was 67 years old (MCI 57–72), in group 2 it was also 67 years old (MCI 62–71) ($p > 0.05$).

The medians of ESR and CRP levels before surgery did not differ significantly between the groups 1 and 2 and amounted to 16 mm/h (MCI 14–27) and 19 mm/h (MCI 13–34) ($p > 0.05$), respectively, 3.0 mg/ml (MCI 1.47–6.2) and 3.3 mg/ml (MCI 1.8–5.8) ($p > 0.05$).

The portion of patients in whom both markers of inflammation were elevated before surgery was 6.1 and 8.5 %, respectively, in groups 1 and 2 ($p > 0.05$). In the overwhelming majority of patients, the material for MBI was obtained before surgery (Fig. 2), however, in more than half of the patients (62.2 %, n = 56), the obtained aspirate did not meet the requirements for the CI, which significantly limited the diagnostic significance of this method.

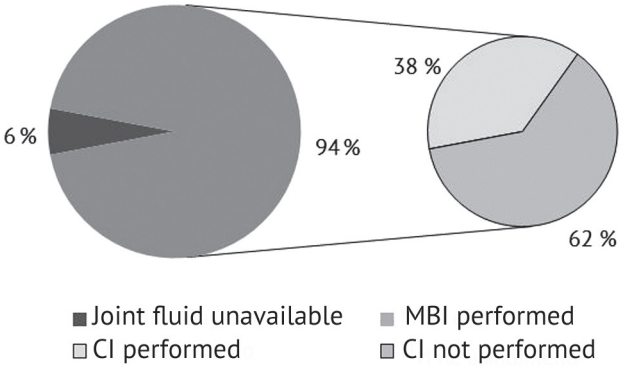

Fig. 2 Rates of aspirate availability for MBI and CI

The evaluation of the CI results showed that the majority of cases (85.3 %, n = 29) were characterized by a normal cytological composition of the aspirate. At the same time, in group 1, in 14.3 % of cases (n = 3 out of 21), the results obtained corresponded to the criterion of confirmed PJI and one case in each group corresponded to probable PJI (infection likely). According to the results of MBI of the intraoperative biomaterial in both groups, coagulase-negative staphylococci were leading, while, in most cases (70.4 %), the diagnostic significance of the results obtained was low (Table 2).

Microbial associations were detected in group 1 in 4.1 % (n = 2) and in group 2 in 6.4 % of cases (n = 3). Microbiologically, the diagnosis of PJI was established only in 8.2 % (n = 4) of patients from group 1 and in 12.8 % (n = 6) of patients from group 2. By comparing the results of MBI of various types of intraoperative biomaterials for isolating the pathogen, the study of tissue biopsies was of decisive importance (Table 3). At the same time, the chances of isolating a diagnostically significant pathogen are 5.6 times higher by studying tissue biopsies in comparison with intraoperative aspirate (OR = 5.6, 95 % CI = 1.2-26.4). However, contaminated microflora is also significantly more often isolated from tissue samples (OR = 5.88, 95 % CI = 1.9-17.9).

Of the entire cohort of patients, it was not possible to obtain an aspirate 6.3 % (n = 6). But in one case a positive growth of *Candida parapsilosis* from intraoperative aspirate and from 5 tissue biopsy specimens was detected. Another patient had *S. saprophyticus* strain in the intraoperative aspirate.

Among patients with negative MBI results of preoperative aspirate (n = 90), growth of microorganisms from intraoperative biomaterial was obtained in 24.4 % (n = 22) of cases, of which the pathogen was diagnostically significant in 40.9 % (n = 9) of cases. The chances of isolating the pathogen from intraoperative material increased more than 4-fold in patients with a combined elevation of ESR and serum CRP, but this was statistically insignificant (OR = 4.686, 95 % CI = 0.765-28.700).

Table 2

Results of intraoperative biomaterial microbiological tests

Agent	Group 1, n = 49			Group 2, n = 47		
	total n (%)	Incl. DS* n (%)	p, value	total n (%)	Incl. DS* n (%)	p, value
Coagulase-negative staphylococci (MRSE, MSSE, *S. saprophyticus*)	7 (14.3)	2 (4.1)	> 0.05	12 (25.5)	4 (8.5)	> 0.05
Anaerobes (*Propionibacterium* and other)	1 (2)	0	> 0.05	4 (8.5)	0	> 0.05
Gram (–)	1 (2)	0	> 0.05	0	0	> 0.05
Candida parapsilosis	1 (2)	1 (2)	> 0.05	0	0	> 0.05
Streptococcus oralis	0	0	> 0.05	1 (2.1)	1 (2.1)	> 0.05

Notes: DS – diagnostically significant

Table 3

Positive growth of pathogens in various intraoperative biomaterials

Intraoperative biomaterial	Group 1, n = 49			Group 2, n = 47		
	Total n (%)	Incl. DS* n (%)	p, value	total n (%)	Incl. DS* n (%)	p, value
Periprosthetic tissues	9 (18.4)	4 (8.2)	> 0.05	12 (25.5)	6 (12.8)	> 0.05
Aspirate	2 (4.1)	1 (2)	> 0.05	2 (4.3)	1 (2.1)	> 0.05
Sonication fluid	0	0	> 0.05	2 (4.3)	1 (2.1)	> 0.05

Notes: DS – diagnostically significant

According to EBJIS criteria, PJI was confirmed in more than 10 % of cases in each group (Table 4). At the same time, probable infection was detected almost 2 times more often in the group of patients with spacers.

The diagnostic specificity of the screening methods studied was high (Table 5), but the sensitivity of serum inflammation markers in both groups was low. The CI sensitivity was high only in patients without a history of infection (group 1). The combination of different methods for detecting PJI using the EBJIS criteria demonstrated high sensitivity and specificity.

The follow-up study was available for 43 patients in group 1 and 43 patients in group 2. The analysis of the outcomes showed that the groups were comparable in terms of treatment efficacy: success was achieved in 95.3 % of patients, regardless of the study group. However, it should be noted that the majority of patients in group 1 received a short course of antibiotic prophylaxis, while patients in group 2 received combined long-term antibiotic therapy (Fig. 3). Regardless of the group, clinical manifestations of PJI after revision were detected in 4.7 % of cases.

In group 1, infection was confirmed using the EBJIS criteria in 5 cases, of which at the time of the follow-up 3 patients had no manifestations of PJI (Table 6). Two patients with diagnostically significant pathogens detected in the intraoperative material had ABT in the early postoperative period. In two more cases, the signs of PJI were found within a manifestation period of 1 and 6 months after revision.

In group 2, two patients had symptoms of PJI more than a year after revision TKA. At the time of TKA, according to the EBJIS criteria, infection was unlikely in them, which may indicate the development of subsequent reinfection, and not a recurrence. Patients of this group with likely (n = 9) and confirmed (n = 4) according to the EBJIS criteria PJI at the time of the follow-up or remote questioning did not need repeated interventions and did not have any clinical and laboratory signs of infection, which indirectly confirms the need for efficient antibiotic therapy at the second stage of surgical treatment of those patients.

Table 4

Allocation of patients with suspected PJI according to EBJIS 2021 criteria

Group	Infection unlikely, n (%)	Infection likely, n (%)	Infection confirmed, n (%)	p, value
1, n = 49	37 (75.5)	6 (12.2)	6 (12.2)	> 0.05
2, n = 47	32 (68)	10 (21.3)	5 (10.7)	> 0.05
Всего	69 (71.9)	16 (16.7)	11 (11.4)	> 0.05

Table 5

Diagnostic significance of laboratory screening results and EBJIS 2021 criteria relative to MBI of intraoperative biomaterial for detecting latent PJI

Markers	> ESR and CRP		Citosis and % PMN		EBJIS 2021	
Group	1	2	1	2	1	2
Sensitivity (%)	33.3	20	100	0	100	100
Specificity (%)	95.7	92.9	90.5	100	92.5	100

Notes: ESR – erythrocyte sedimentation rate; CRP – c-reactive protein; PMN – polymorphonuclear neutrophils

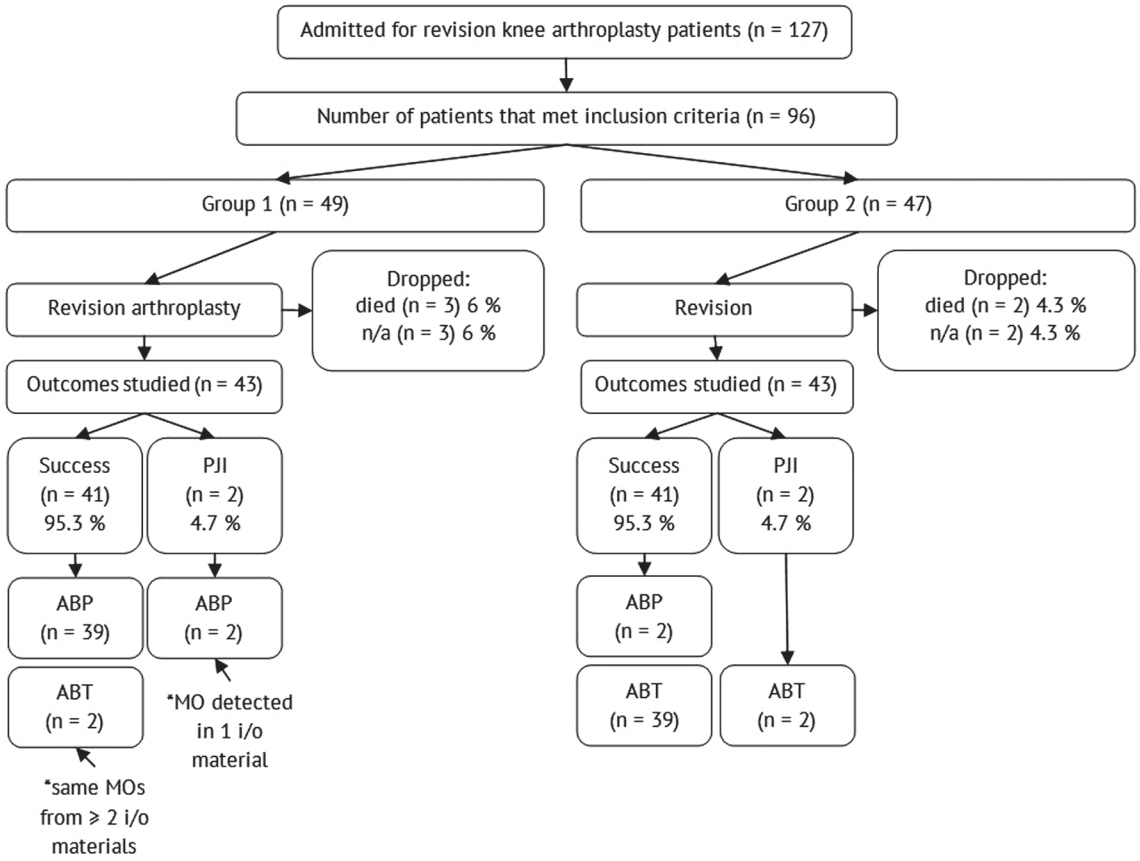

Fig. 3 Late outcomes of revision knee arthroplasty in patients in the comparison groups: n/ a – not available; MO – microorganisms; i/o – intraoperative

Table 6

Follow-up outcomes of knee revision arthroplasty according to EBJIS 2021 criteria diagnosis

Outcome	Group 1, n = 49				Group 2, n = 47			
	PJI unlikely	PJI likely	PJI confirmed	p, value	PJI unlikely	PJI likely	PJI confirmed	p, value
Success	34	4	3	< 0.001	28	9	4	> 0.05
PJI	0	0	2	< 0.001	2	0	0	> 0 .05
Total	34	4	5		30	9	4	

Notes: PJI – periprosthetic infection

DISCUSSION

The search for an ideal marker for verifying the diagnosis of PJI and identifying persistent infection still continues. Many authors report a high diagnostic value of a combined elevation in various biomarkers, such as ESR, serum CRP, interleukins, fibrinogen, and D-dimer [8–10]. However, according to the results of the Second International Consensus Conference on Musculoskeletal Infection [11], no consensus has been reached on the optimal combination of serum biomarkers. Therefore, ESR and CRP remain the most frequently used markers in the diagnosis of PJI, since their determination is a minimally invasive and accessible procedure in contrast to synovial tests, especially with an implanted spacer, when in some cases the aspirate material is not available. Despite the proven efficacy of ESR and CRP in serum for detecting PJI, the diagnostic significance of these tests for assessing the effectiveness of the debridement stage of PJI treatment has not been adequately studied. Thus, a number of publications argue that ESR and CRP have limitations in detecting a recurrence of PJI or reinfection before revision arthropalsty [12–15].

Other authors also report a low sensitivity of serum CRP in predicting the effectiveness of debridement before revision arthroplasty [16–19]. Hoell S. et al. (2016) estimate the diagnostic sensitivity of serum CRP at 42.1 %, and the specificity at 84.2 % [19]. On the other hand, a number of researchers who evaluated the combined elevation in ESR and CRP between the stages of a two-stage revision report 100 % sensitivity [20]. However, according to other authors, the combined elevation in ESR and serum CRP has a sensitivity and specificity of 78.8 to 89 % [15, 17, 21]. Our study showed a lower sensitivity of the simultaneous increase in serum biomarkers, 33.3 % in group 1 and 20 % in group 2, with a slightly higher specificity of 95.7 % and 92.9 %, respectively. However, despite the lack of statistical significance, the combined elevation in ESR and serum CRP by more than 4 times (OR = 4.686, 95 % CI = 0.765–28.700) increased the chances of isolating the pathogen from the intraoperative material.

High sensitivity and specificity in the PJI diagnosis in patients without a history of infectious complications is demonstrated by an increase in the number of leukocytes and the proportion of PMN in the preoperative aspirate from the joint cavity [22-28]. A recent meta-analysis of ten studies showed that increased leukocyte counts in the SF have a sensitivity of 90.0 % (95 % CI 87.2–92.2 %) and a specificity of 89.8 % (95 % CI 81.4–94.7 %) [29]. Similar results were obtained in our study, the group of patients with non-infectious causes of revision had CI sensitivity of 100 %, the specificity of 90.5 %. Aspirate CI is a reliable method for detecting new PJI [30]; however, a number of authors report its low sensitivity when assessing the effectiveness of sanitation before revision arthroplasty. Thus, Mühlhofer H.M.L. et al. (2017) found that the CI of a joint aspirate with a spacer has a sensitivity of 10 %, which makes it difficult to diagnose persistent infection in patients between treatment stages [16]. The same conclusions can be drawn from the results of our study. In patients with an implanted spacer due to PJI, the CI of the aspirate turned out to be an absolutely insensitive method (0 %), although highly specific (100 %). However, this could be due to the small number of cases.

To date, there is not a single diagnostic test that has 100 % sensitivity and specificity. Comparative analysis of the diagnostic value, accuracy and specificity of the diagnostic MSIS algorithms (Society of Musculoskeletal Infection, 2018), WAIOT (World Association for Infection Control in Traumatology and Orthopedics) and EBJIS (European Society of Bone and Joint Infections, 2018), conducted by Kazantsev DI et al. (2020), showed the highest accuracy of the MSIS criteria (91.3 %), the best specificity of the WAIOT and MSIS algorithms (95.8 %) [31]. Martin McNally et al. (2021) reported the results of a project developed by EBJIS in conjunction with MSIS and ESCMID (European Society for Clinical Microbiology and Infectious Diseases), which resulted in revised PJI criteria [7]. According to the results of our study, the EBJIS criteria (2021) turned out to be highly sensitive and highly specific methods for detecting PJI, and the selection of the "PJI is likely" group allows one to think about a possible latent infectious process. To date, confirmation or exclusion of the diagnosis of PJI in such cases is delayed based on the results of the MBI of the intraoperative material, which does not allow timely changes in the tactics of surgical treatment and postoperative management of the patient. In addition, even with negative screening results before revision (study of ESR and CRP, CI and MBI), up to 15 % of cases show the growth of a microorganism from only one sample of intraoperative biomaterial (Coventry-Tsukayama IV type PJI) [32–33].

According to many authors, urgent histological study of periprosthetic tissues has been considered a highly specific method that has a better correlation with the final clinical diagnosis than MBI [27, 34–37]. This method may confirm or exclude the diagnosis of PJI intraoperatively and promptly adjust the treatment tactics. Thus, according to Qiao J. et al. (2021), a positive result of urgent histological study of frozen periprosthetic tissues at the revision stage was independently associated with the subsequent recurrence of PJI, despite normal ESR and CRP levels prior to revision [38]. Recurrence of PJI occurred in 8 (30.77 %) of 26 patients with positive histology at the revision stage, compared with 13 (9.49 %) of 137 patients with negative histological results. In addition, in positive histology, the risk of failure increased almost 5-fold (OR = 4.70; 95 % CI, 1.64 to 13.45). In our study, all cases with probable PJI according to EBJIS criteria in group 2 patients turned out to be false-positive, but this may be due to the effectiveness of prolonged antibiotic therapy after revision. For patients with spacers, there is currently no system for verifying the recurrence of PJI or reinfection, and it is not possible to accurately assess the diagnostic significance of this algorithm at the revision stage, since adequate debridement and lavage at the stage in combination with subsequent systemic ABT could lead to no growth of untreated PJI, which requires further research. Possibly, two cases of a detected late infection in patients with an unlikely PJI according to the EBJIS criteria could have been prevented if an urgent histological study of periprosthetic tissues was included in the examination complex, which would enable to timely adjust the treatment tactics.

Limitations of study

The limitations include the retrospective nature of the study, the consequence of which is the absence of the results of an urgent histology. The small number of patients included in the comparison group was compensated by strict criteria for inclusion in the study and adequate statistical methods for processing the data obtained.

CONCLUSION

Thus, the routine study of ESR and CRP in patients admitted for knee RA may identify a risk group with a high likelyhood of isolating the pathogen from intraoperative biomaterial. A preoperative study of the cytological composition of the aspirate in patients with an implanted spacer showed an extremely low sensitivity, which casts doubt on the advisability of routine use of this study in patients with a spacer. EBJIS 2021 criteria are characterized by high diagnostic sensitivity and specificity and enable to identify periprosthetic joint infection in knee revision cases even in its latent form and to correct treatment tactics in patients without its history. Apparently, conducting an emergency intraoperative histological study of periprosthetic tissues during RA accelerate the detection of PJI and, accordingly, in an adequate time frame, prescribe empirical antibiotic therapy, which can be corrected already upon receiving the results of a microbiological study of intraoperative materials.

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Information about the authors:

1. Alexander N. Panteleev – M.D., alex.pant95@mail.ru
2. Svetlana A. Bozhkova – Doctor of Medical Sciences;
3. Petr M. Preobrazhensky – Candidate of Medical Sciences;
4. Alexander V. Kazemirsky – Candidate of Medical Sciences.

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