

## Protein Energy Malnutrition as a Predictor of Early Recurrent Revisions After Debridement Surgery in Patients With Difficult-to-Treat Periprosthetic Infection

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**Background.** Protein energy malnutrition (PEM) is a proven risk factor of postoperative complications in orthopedic patients, including arthroplasty of the large joints. **The aim** of our study was the evaluation of PEM prevalence and its association with the early postoperative revision in patients with the difficult-to-treat (DTT) prosthetic joint infection (PJI) of the hip. **Methods.** The retrospective study included 132 patients with chronic DTT PJI of the hip. The patients underwent the removal of the orthopedic implant, radical debridement of the infected tissues, and resection arthroplasty with non-free transplantation of an axial vastus lateralis muscle flap (n = 57) or installation of an antimicrobial spacer (n = 75). DTT PJI was defined as infection caused by rifampicin-resistant staphylococcal strains, ciprofloxacin-resistant gram-negative bacteria, fungi of the genus *Candida*, as well as their associations. Assessment of the patient's protein-energy status included the evaluation of the reference laboratory parameters: the levels of hemoglobin, total protein, albumin, and the number of lymphocytes. The degree of PEM was determined by the number of laboratory markers below the threshold values. The statistical comparison was performed using Fisher's test. The odds ratio (OR, 95% CI) was calculated to assess the risk of PJI recurrence. Differences were considered significant at p < 0.05. **Results.** More than 70% of patients with chronic DTT PJI included in the study were diagnosed with preoperative PEM of varying degree of severity. Hypoalbuminemia and a decrease in hemoglobin levels were diagnosed more often: 64.3% and 57.1% in the muscle flap plasty and 57.3% and 31.1% in the antimicrobial spacer group, respectively. In addition, in muscle plasty and antimicrobial spacer groups, a decrease of three or more reference PEM markers was detected in 28.5% and 16.0% of patients and this advanced impairment of the nutritional status increased the risk of early revision intervention by 2 (OR 2.0; CI 95% 0.47–8.56; p = 0.35) and 6 times (OR = 6.11; CI 95% 1.06–35.35; p < 0.04), respectively. **Conclusion.** In general, the analysis of publications and results of our study show that PEM is associated with the development of surgical site infection and recurrence of PJI after revision surgery. A decrease in three or more reference PEM markers is a significant predictor of repeated revisions after debridement surgery with the installation of an antimicrobial spacer. PEM complicates the course of postoperative period in patients with resection arthroplasty. Given the high incidence of PEM in patients with DTT PJI of the hip joint further research is needed to develop methods for nutritional status correction and assessment of their impact on the outcomes of debridement surgery.

**Keywords:** difficult-to-treat infection, prosthetic joint infection, protein energy malnutrition, hip resection arthroplasty.

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## Белково-энергетическая недостаточность как предиктор ранних повторных ревизий после санирующих операций у пациентов с трудноизлечимой перипротезной инфекцией

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**Введение.** Белково-энергетическая недостаточность (БЭН) является доказанным фактором риска развития послеоперационных осложнений у ортопедических больных, в том числе и после эндопротезирования крупных суставов. **Целью** исследования была оценка частоты встречаемости БЭН и ее влияния на необходимость выполнения ревизионного вмешательства в раннем послеоперационном периоде у пациентов с трудноизлечимой (ТИ) перипротезной инфекцией (ППИ) тазобедренного сустава. **Материал и методы.** В ретроспективное исследование включено 132 пациента с хронической ТИ ППИ тазобедренного сустава, которым были выполнены удаление ортопедического имплантата, радикальная хирургическая обработка очага инфекции и резекционная артропластика с несвободной пересадкой осевого мышечного лоскута из *m. vastus lateralis* ( $n = 57$ ) или установка антимикробного спейсера ( $n = 75$ ). К ТИ ППИ относили инфекцию, обусловленную рифампицин-резистентными штаммами стафилококков, цiproфлоксацин-резистентными штаммами грамотрицательных бактерий, грибами рода *Candida*, а также их ассоциациями. Оценка белково-энергетического статуса пациента включала определение опорных лабораторных показателей: уровней гемоглобина, общего белка, альбумина и количество лимфоцитов. Степень БЭН определяли по количеству лабораторных маркеров ниже пороговых значений. Сопоставление относительных показателей сравнения выполняли с применением критерия Фишера. Для оценки влияния БЭН на развитие рецидива рассчитывали отношение шансов (ОШ, 95% ДИ). Различия принимали за достоверные при  $p < 0,05$ . **Результаты.** Более чем у 70% больных с хронической ТИ ППИ, включенных в исследование, до операции была диагностирована БЭН различной степени тяжести. Чаще диагностировали гипоальбуминемию и снижение уровня гемоглобина: соответственно 64,3% и 57,1% в группе мышечной пластики и 57,3% и 31,1% в группе антимикробного спейсера. В группах мышечной пластики и антимикробного спейсера дефицит трех и более опорных показателей БЭН был выявлен соответственно у 28,5% и 16,0% пациентов, при этом наличие таких выраженных нарушений нутриционного статуса увеличивало риск раннего ревизионного вмешательства в 2 раза (ОШ = 2,0; ДИ 95% 0,47–8,56;  $p = 0,35$ ) и в 6 раз (ОШ = 6,11; ДИ 95% 1,06–35,35;  $p < 0,04$ ). **Заключение.** Анализ научных публикаций и результаты нашего исследования показывают, что БЭН связана с развитием ИОХВ и рецидивом ППИ после ревизионных операций. Снижение трех и более опорных показателей БЭН является значимым предиктором повторных ревизий после санирующих операций с установкой антимикробного спейсера, а также ухудшает течение раннего послеоперационного периода у пациентов с резекционной артропластикой. С учетом высокой частоты встречаемости БЭН различной степени тяжести у пациентов с ТИ ППИ тазобедренного сустава необходимы дальнейшие исследования по разработке методов коррекции нутриционного статуса и оценке их влияния на исходы санирующих операций.

**Ключевые слова:** трудноизлечимая инфекция, перипротезная инфекция, белково-энергетическая недостаточность, резекционная артропластика, тазобедренный сустав.

### Introduction

Chronic prosthetic joint infection (PJI) is one of the serious complications of total joint arthroplasty. The worst treatment results are observed in infections caused by drug-resistant strains of bacteria [1, 2]. Lately, the so-called difficult-to-treat (DTT) infection has been defined as an infection caused by difficult-to-eradicate pathogens such as rifampicin-resistant staphylococci, ciprofloxacin-resistant gram-negative bacteria and *Candida* fungi [3]. Multiple attempts to eradicate this infection through

debridement surgery result in large bone defects. Resection arthroplasty of the hip coupled with a flap of vastus lateralis muscle filling the bone defect has been shown as an effective way to achieve the control of infection, particularly, in case of the DTT PJI and in some cases restore its function [4, 5]. This surgical approach improves the blood supply and the delivery of oxygen, leucocytes and antibiotics to the affected tissue which helps to eradicate pathogens responsible for the chronic infection decreasing the risk of PJI recurrence [6].

The imbalance of nutrients or protein-energy malnutrition (PEM) is one of the main causes of increased morbidity and mortality, reduced quality of life, increased frequency and length of hospital stay, and associated health care costs [7, 8]. PEM is a proven risk factor for the development of postoperative complications in orthopedics including patients who underwent arthroplasty of large joints as well as spinal surgery [9, 10, 11]. In addition, PEM not only negatively affects postoperative recovery and wound healing but also increases the risk of early and late surgical site infection [12]. The incidence of PEM in orthopedic patients requiring arthroplasty varies from 8.5% to 50% [13, 14, 15]. PEM has been shown both as a risk factor for the onset of prosthetic joint infection and a predictor of the infection recurrence after primary arthroplasty [16]. Surrogate markers of PEM such as total lymphocyte count, serum albumin and transferrin have been extensively used to assess the underlying nutritional status of patients [17, 18]. Increased risk of complications after total hip arthroplasty including the recurrence of PJI has been associated with hypoalbuminemia [19]. Low levels of albumin in combination with hemoglobin were also associated with the development of PJI [18].

The number of studies that have addressed the role of PEM in the development of PJI is limited. Most of them are hindered by heterogeneous cohorts without any discrimination between cases of primary and revision arthroplasty, or PJI and trauma-related surgery [15, 20]. Given this, we aimed to evaluate the prevalence of PEM in patients DTT PJI of the hip. In addition, the association of preoperative PEM with surgical complications requiring early postoperative revision after resection arthroplasty with a muscle flap or a cement spacer implantation was assessed.

### Methods

The data for the study were retrieved from the records of the local PJI register covering the period of 2012–2018. The study was approved by the institutional review board. General informed consent was obtained as a part of the hospital admission.

Of all 132 patients included in the study, 57 were treated with a pedicled muscle flap after the removal of the endoprosthesis. Surgical debridement of the affected tissue was followed by subsequent transplantation of a vastus lateralis muscle flap of the femur retaining the vascular supply. Alternatively, the remaining 75 patients were treated with surgical debridement and installation of an antimicrobial cement spacer in place of the metal components.

The main inclusion criteria were chronic DTT PJI of the hip caused by rifampicin-resistant staphylococci, ciprofloxacin-resistant Gram-negative bacteria and/or Candida fungi. The main laboratory parameters which were taken for the evaluation of the nutritional status

included total lymphocyte count, hemoglobin, albumin and total protein. The cut-off values suggesting PEM were defined as follows: total lymphocyte count (TLC) at  $<1.5 \times 10^9$  cells/L, hemoglobin at  $<12.0$  g/dL, albumin at  $<3.5$  g/dL and total protein at  $<6.5$  g/dL. The severity of PEM was defined as the percentage of cases with one, two or three and more of these laboratory values below the cut-off level.

Postoperatively, all patients received intravenous antibiotic therapy followed by oral antibiotics for 6–8 weeks. The proportion of patients requiring revision surgery in the early postoperative period was evaluated regardless of the cause.

### Statistic analysis

The data were analyzed using Statistica v10 (StatSoft, Russia) and GraphPad Prism v 9.0 (GraphPad, USA). Categorical variables are shown as percentages. They were evaluated using Fischer's exact test. Odds ratios (OR) were calculated with respective confidence intervals (CI) at the confidence level of 95%. The P-value below 0.05 was considered as the indication of statistical significance.

### Results

General characteristics of the cohort are depicted in Figure 1. Patients treated with a muscle flap had a longer median duration of PJI and a lower percentage of at least two episodes of infection recurrence before the hospital admission as compared to patients managed using two-stage revision with a cement spacer.

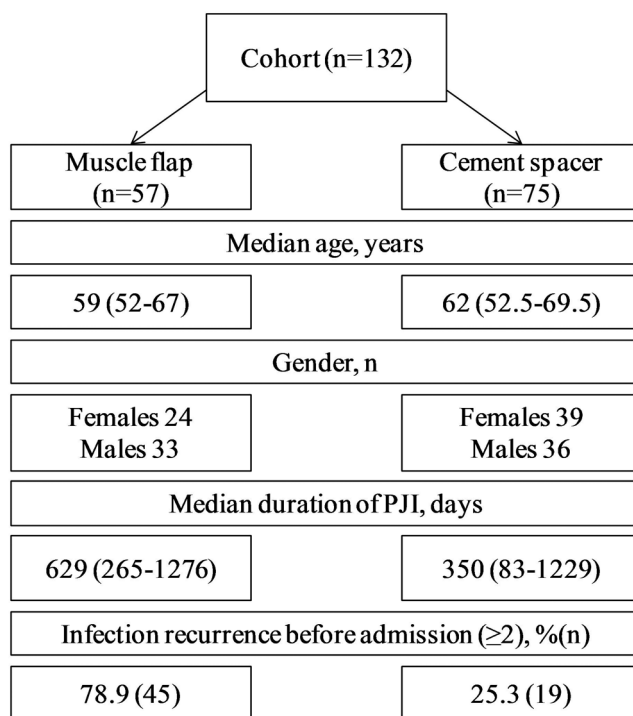


Fig. 1. General characteristics of the cohort

Fig. 1. Общая характеристика пациентов

Hypoalbuminemia and decreased hemoglobin were the most common markers of malnutrition in the cohort (Fig. 2).

Whereas the overall fraction of patients with one abnormal malnutrition marker was comparable to those without PEM in the muscle flap group but higher in the cement spacer group (Fig. 3).

Association of the advanced malnutrition (at least three abnormal markers) and post-operative complications requiring surgical revision was only statistically evident in the cement spacer group (Fig. 4, 5).

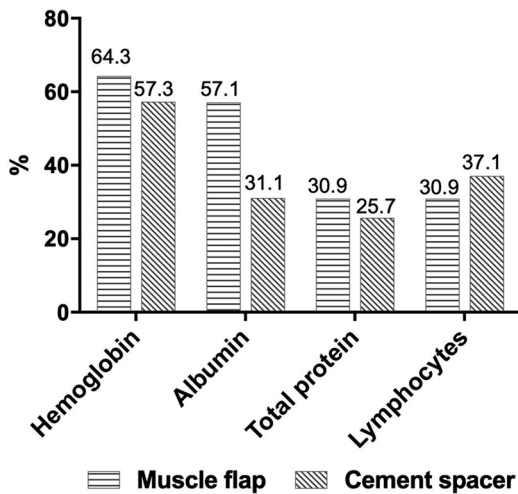


Fig. 2. Percentage of the decreased surrogate markers of PEM in the cohort

Рис. 2. Доля пациентов со снижением уровня опорных показателей БЭН в группах сравнения

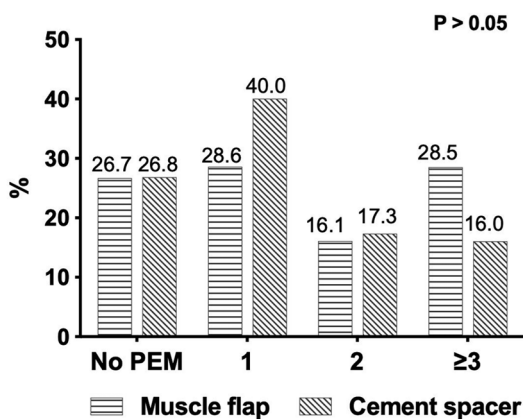


Fig. 3. Severity of the preoperative PEM

Рис. 3. Частота встречаемости БЭН различной степени выраженности у пациентов групп сравнения

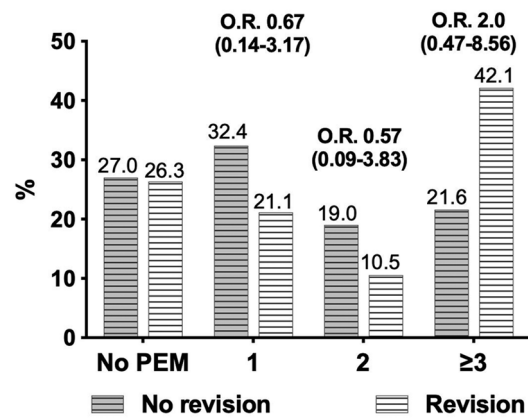


Fig. 4. Association of PEM and revision surgery in the muscle flap group

Рис. 4. Влияние степени выраженности БЭН на течение раннего послеоперационного периода в группе мышечной пластики

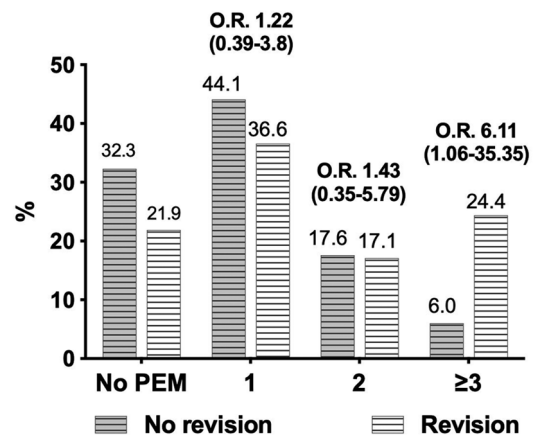


Fig. 5. Association of PEM and revision surgery in the cement spacer group

Рис. 5. Влияние степени выраженности БЭН на течение раннего послеоперационного периода в группе антимикробного спейсера

### Discussion

Despite the worse functional outcomes compared to the use of an antimicrobial spacer, resection arthroplasty of the hip joint using a vastus lateralis muscle flap is an effective procedure to achieve PJI control [4]. The cohort of patients in the present study has previously been assessed to compare the efficacy of resection arthroplasty with a muscle flap and a cement spacer implantation for treatment of DTT PJI [5]. In all patients with the muscle flap and cement spacer, the infection remission was achieved in 96.5% (n = 55) and 45.3% (n = 34) of cases, respectively. Late recurrence of PJI was only in 2.5% (n = 2) of cases with the muscle flap vs 26.7% (n = 20) of cases with a cement spacer. Thus, resection arthroplasty with a vastus lateralis muscle flap proved to be a strategy of choice for management of recurrent DTT PJI. In contrast, for this

study, the cohort was analyzed both for the prevalence of preoperative PEM and the association of PEM with early postoperative complications requiring revision.

The average preoperative prevalence of PEM in patients undergoing arthroplasty depending on the heterogeneity of the cohort has been widely reported at 8.5%, 12.3%, 53% and 80% [13, 15, 15, 20, 21]. At the time of hospital admission, most of our patients (>70%) had laboratory signs of PEM. It is well known that prolonged systemic inflammatory response due to the persistent infection eventually leads to the loss of muscle mass and function, which could itself be the manifestation of PEM [7, 8]. For instance, cases of revision arthroplasty due to septic complications had a higher rate of hypoalbuminemia as compared to aseptic cases [10]. Given this, it is feasible to assume that long-term chronic DTT PJI with multiple prior failed revisions could have been the primary reason for the impaired preoperative nutritional status of our patients. This would also explain the rather high prevalence of PEM in our study compared to previous reports. It is noteworthy to mention that the already abnormal nutritional status of patients at the time of hospital admission could have also been further aggravated by the surgery.

Several laboratory values have been considered as surrogate markers for the early diagnosis of PEM. For instance, albumin and hemoglobin have been shown as independent factors associated with PJI occurrence after primary elective THA [18]. Whereas albumin had the highest specificity and a positive predictive value compared to all other markers such as total lymphocyte count and transferrin. Other studies have also confirmed the association of hypoalbuminemia with complications of arthroplasty from surgical site infection to pneumonia, cardiovascular pathology, and urinary tract infection [9, 21, 22, 23]. Like the above reports, our findings showed low albumin and hemoglobin as the most prevalent (>50%) abnormal laboratory values.

Our previous study showed that in the early postoperative period, the only indication for the secondary revision in the spacer group (28%, n = 21) was the recurrence of the infection. Alternatively, main indications (35%, n = 20) for post-operative revision in the muscle flap group were necrosis of the flap (8.8%, n = 5), culture-negative hematomas (10.5%, n = 6), and recurrence of the infection including

wound dehiscence or prolonged wound drainage for more than 7 days (15.7%, n = 9) [5]. PEM was found to be associated with the prolonged surgical site discharge and subsequent deep infection which required additional treatment after elective total joint arthroplasty [16]. In our cohort, a decrease of 3 or more laboratory markers of PEM increased the risk of postoperative wound revision by 6 times in patients with a cement spacer (OR 6.11, CI95% 1.06–35.35, P<0.04) and 2 times in patients with a muscle flap (OR 2.0, CI95% 0.47–8.56, P = 0.35) (see Fig. 4, 5).

Due to the retrospective nature of our study, some medical records such as BMI index and a complete list of concomitant pathology were missing for a part of the cohort and thus were omitted from the analysis.

Enteral nutrition is a process of providing the patients with necessary supplements has been long regarded as a method of choice for PEM correction in general medicine and hip replacement in geriatric patients [24]. Unfortunately, due to the limited number of studies addressing potential benefits of PEM correction in orthopedic patients the exact guidelines for preventing early post-operative complications including PJI recurrence via nutritional supplementation before and after arthroplasty are yet to be established. In a clinical study of 162 cases of primary knee arthroplasty, it has been shown that patients with constant perioperative nutritional management had a lower number of postoperative complications such as wound drainage, hematomas, superficial and deep infection as well as the reduced number of albumin transfusions and a shorter hospital stay [25]. This suggests that implementing the protocols for hypoproteinemia correction before any major orthopedic surgery such as primary and revision arthroplasty including patients with PJI could improve its outcome.

Overall, both previous reports and our data show that malnutrition is associated with the occurrence of surgical site infection and relapse of PJI after revision arthroplasty. In particular, the risk of postoperative revision was significantly associated with multiple pathological markers of PEM in two-stage revision with a cement spacer but not with a muscle flap surgery. Considering the mounting evidence that malnutrition is a modifiable risk factor for PJI, more studies are required to demonstrate the efficacy of preoperative PEM correction.

## Disclaimers

### Authors' contributions

*Svetlana A. Bozhkova* — research concept and design, data statistical processing, manuscript writing and editing.

*Vitaly N. Liventsov* — data collection and analysis, manuscript writing.

## Дополнительная информация

### Заявленный вклад авторов

*Божкова С.А.* — идея и дизайн исследования, написание и редактирование текста статьи, интерпретация полученных данных.

*Ливенцов В.Н.* — сбор, статистическая обработка данных, интерпретация полученных данных, написание текста статьи.

*Rashid M. Tikhilov* — research concept and design.

*Carlo L. Romano* — research concept and design, final manuscript editing.

*Aleksandr Yu. Kochish* — research concept and design.

*Dmitry V. Labutin* — data statistical processing, manuscript writing.

*Vasily A. Artyukh* — treatment the patients, manuscript editing.

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.

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**Competing interests.** The authors declare that they have no competing interests.

**Ethics approval.** Not applicable.

**Consent for publication.** Not required.

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