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Experimental Medicine

Risk Factors for Periprosthetic Knee Infection Recurrence after Two-Stage Reimplantation: Differential Treatment Approach

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Abstract. Periprosthetic joint infection (PJI) is a challenging knee arthroplasty complication with controversial criteria for second-stage revision timing. This study developed a differential approach to optimize surgical treatment selection and identify successful reimplantation predictors. A retrospective analysis of a total of 40 patients undergoing two-stage revision knee arthroplasty for PJI (2014-2024). Laboratory, microbiological, radiological, and functional parameters were evaluated. A scoring system for predicting second-stage outcomes was developed, which achieved 90% prediction accuracy with significant functional improvement differences between risk groups. © *2025 Bull. Georg. Natl. Acad. Sci.*

Keywords: periprosthetic infection, knee joint, two-stage revision arthroplasty, antibiotic spacer, C-reactive protein

Introduction

Periprosthetic joint infection (PJI) is one of the most frequent and dangerous complications of total knee arthroplasty (TKA), occurring in approximately 1-2% of primary arthroplasty cases and up to 4% of revision procedures (Albagly et al., 2024; Andres et al., 2024). Despite improvements in surgical techniques, antibiotic prophylaxis, and infection control measures, the incidence of PJI continues to rise alongside the increasing number of arthroplasty procedures.

Two-stage revision arthroplasty remains the "gold standard" for treating chronic PJI in most orthopedic centers worldwide (Lozano et al., 2022; Chang et al., 2018). This method involves removal of the infected prosthesis, debridement of infected tissues, implantation of an antibiotic spacer in the first stage, and reimplantation of a new prosthesis after infection eradication in the second stage (Wignadasan et al., 2023). Although success rates of two-stage revision arthroplasty reach 80-90%, many aspects of this treatment strategy remain controversial (Vielgut et al., 2021).

One key issue is determining the optimal timing for performing the second stage of reimplantation and reliable criteria for infection eradication. Traditionally, normalization of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels, along with absence of pathogens in joint aspirate, are considered important criteria for confirming infection eradication (Zhang et al., 2024). However, the reliability of these criteria and their prognostic value regarding second-stage arthroplasty success require further investigation.

The aim of our study was to improve knee arthroplasty outcomes in patients with PJI sequelae by developing a differential approach to selecting optimal surgical treatment methods and identifying predictors of successful second-stage reimplantation in the context of infection eradication and functional outcomes.

Materials and Methods

Study design and patient selection. A retrospective analysis of medical records of patients who underwent two-stage revision knee arthroplasty for PJI at the Institute of Traumatology and Orthopedics of NAMS of Ukraine from January 2014 to December 2024 was conducted. The study was approved by the institutional ethics committee.

Inclusion criteria: Confirmed PJI according to Musculoskeletal Infection Society (MSIS) criteria; Completed two-stage revision arthroplasty; Minimum follow-up period of 12 months after second-stage reimplantation.

Exclusion criteria: Single-stage revision arthroplasty; Resection arthroplasty without subsequent reimplantation; Incomplete medical documentation.

A total of 40 patients meeting the aforementioned criteria were included in the study.

Surgical technique and clinical protocol. All patients underwent standard two-stage revision arthroplasty:

First stage: Removal of infected prosthesis; Radical debridement of infected tissues with specimen collection for microbiological examination; Antibiotic spacer implantation Post-operatively, patients received antibiotic therapy according to microbiological results for 4-6 weeks.

Before second stage: Assessment of inflammatory laboratory markers (CRP, ESR); Joint aspiration with microbiological examination of synovial fluid; Radiological evaluation of knee joint status.

Second stage: Spacer removal; Repeat debridement; Revision prosthesis implantation using a differential approach to implant selection; Collection of intraoperative specimens for microbiological examination.

Here's the condensed version:

Outcome assessment. Primary endpoint: successful infection eradication (absence of clinical, laboratory, and radiological infection signs). Secondary endpoints: functional outcomes (KSS, OKS), complications, reinfection risk factors, and quality of life (SF-36).

Laboratory studies. Comprehensive investigations included: biochemical markers (CRP, fibrinogen), immunological parameters (leukocyte count, ASO), serological studies (RF), and synovial fluid bacterial cultures.

Baseline assessment. Post-first-stage evaluation included standard radiography and clinical assessment of joint stability and mobility.

Prediction system. A scoring system was developed using laboratory parameters (CRP, ESR, ASO), microbiological data (pathogen type, antibiotic sensitivity), clinical characteristics (sinus tract presence, spacer duration), and comorbidities to predict second-stage outcomes.

Differential approach. Treatment selection methodology considered reinfection risk, soft tissue condition, and knee joint stability.

Quality of life assessment. SF-36 questionnaire assessed 8 scales: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. Scores were transformed to 0-100 scale and summarized into physical (PCS) and mental (MCS) components, standardized to Ukrainian population

norms (mean 50±10 points). Scores: <40 (low), 40-60 (average), >60 (high).

Statistical analysis. SPSS 25.0 used with Shapiro-Wilk normality testing. Comparisons used paired/unpaired t-tests, Wilcoxon/Mann-Whitney tests, or chi-square tests. Logistic regression identified infection eradication factors ($p<0.05$ significance, stepwise selection $p<0.1$).

Results. Demographic and clinical characteristics. A total of 40 patients (17 men and 23 women) with a mean age of 65.7±9.3 years were included in the study. All patients had knee PJI. Demographic and clinical characteristics are presented in Table 1.

Table 1. Demographic and clinical patient characteristics

Characteristic	Value
Mean age, years	65.7±9.3
Gender, n (%)	
Male	17 (42.5%)
Female	23 (57.5%)
Body mass index, kg/m²	29.3±4.6
Comorbidities, n (%)	
Arterial hypertension and/or IHD	10 (25%)
Rheumatoid arthritis	5 (12.5%)
Ankylosing spondylitis	1 (2.5%)
Other/not specified	24 (60%)
Smoking	7 (17.5%)
ASA* class, n (%)	
I	4 (10%)
II	21 (52.5%)
III	15 (37.5%)
Reason for primary arthroplasty, n (%)	
Primary osteoarthritis	27 (67.5%)
Post-traumatic arthritis	6 (15%)
Avascular necrosis	4 (10%)
Rheumatoid arthritis	3 (7.5%)
Time from primary arthroplasty to PJI diagnosis, months (median, IQR)	18 (9-36)
Presence of sinus tract, n (%)	15 (37.5%)
Causes of PJI development, n (%)	
Glucocorticosteroid injections	6 (15%)
Trauma	6 (15%)
Joint punctures	4 (10%)
Other causes	24 (60%)
Infection type by Tsukayama classification, n (%)	
Type II (early postoperative)	9 (22.5%)
Type III (late chronic)	24 (60%)
Type IV (acute hematogenous)	7 (17.5%)

**ASA = American Society of Anesthesiologists; IQR = interquartile range.*

Microbiological data. Microbiological confirmation was obtained in 36 patients (90%); 4 patients (10%) had negative cultures despite clinical/histological infection signs.

Most frequent pathogens: Staphylococcus aureus (30%), coagulase-negative staphylococci (15%), S. epidermidis (5%), Enterococcus faecalis (5%), Enterobacter sp. (5%), Pseudomonas aeruginosa (2.5%). Polymicrobial infection occurred in 6 patients (15%), gram-negative flora in 7 patients (17.5%). Highest antibiotic sensitivity: vancomycin (92%), ciprofloxacin (74%), clindamycin (68%).

Laboratory Data and Spacer Period

Laboratory parameter dynamics. Median spacer period was 14 weeks (range: 8-32 weeks). Distribution: ≤3 months (15%), 3-6 months (55%), 6-12 months (20%), >12 months (10%).

Before second stage: CRP normalized (<10 mg/L) in 85% of patients, ESR normalized (<30 mm/h) in 80%. Complete normalization of both markers occurred in 75% of patients (Table 2).

Joint aspiration before the second stage was performed in all patients. Positive synovial fluid cultures were obtained in 5 patients (12.5%), requiring continued antibiotic therapy and postponement of the second stage.

Radiological assessment of baseline knee joint status. Radiological examination of knee joints after the first stage revealed:

- Proper spacer position in 36 patients (90%)
- Spacer component subluxation in 4 patients (10%)
- Signs of periarticular osteopenia in 28 patients (70%)

Second-stage outcome prediction system. Based on identified risk factors and success predictors, a scoring system for predicting second-stage arthroplasty outcomes was developed (Table 3).

Table 2. Mean laboratory parameter values during follow-up after first-stage arthroplasty

Parameter	Pre-operative	1 week	2 weeks	≥12 weeks	p-value
CRP (mg/L)	74.5±28.3	42.1±18.7	23.5±12.3	8.4±4.3	<0.001
ESR (mm/h)	67.3±21.4	48.6±16.8	38.2±12.5	19.3±8.6	<0.001
Leukocytes (×10⁹/L)	12.3±3.6	9.8±2.7	8.5±2.2	7.2±1.5	<0.001
Antistreptolysin-O (IU/mL)	525.8±312.6	445.3±253.4	386.7±201.8	275.3±141.2	<0.01
Fibrinogen (g/L)	5.8±1.4	4.3±1.1	3.6±0.9	3.1±0.7	<0.001

Table 3. Scoring system for predicting second-stage arthroplasty outcomes

Factor	Points
Laboratory Parameters	
CRP <10 mg/L	+2
CRP 10-20 mg/L	+1
CRP >20 mg/L	-2
ESR <30 mm/h	+2
ESR 30-50 mm/h	0
ESR >50 mm/h	-2
Microbiological Data	
Negative synovial fluid culture	+3
Previous MRSA infection	-2
Polymicrobial infection	-1
Clinical Characteristics	
Spacer period duration >12 weeks	+2
Spacer period duration 8-12 weeks	+1
Spacer period duration <8 weeks	-1
Presence of sinus tract	-2
Comorbidities	
Rheumatoid arthritis	-1
Diabetes mellitus	-1
Radiological Data	
Proper spacer position	+1
Spacer component subluxation	-1

Result interpretation:

- ≥6 points: Low reinfection risk, standard revision arthroplasty recommended;
- 3-5 points: Moderate reinfection risk, additional assessment and possible second-stage postponement recommended;
- ≤ 2 points: High reinfection risk, second-stage postponement and risk factor correction recommended.

Differential approach to second-stage arthroplasty. Based on the developed prediction system, a differential approach to selecting second-stage arthroplasty methodology was proposed. The differential approach included the following:

A. Patients with low reinfection risk (≥ 6 points):

- Standard revision arthroplasty with possible use of primary implants when ligamentous apparatus is preserved;
- Use of augments only in cases of significant bone defects;
- Minimal postoperative antibiotic therapy duration (7-10 days);

B. Patients with moderate reinfection risk (3-5 points):

- Revision arthroplasty using implants with enhanced stability;
- Mandatory use of antibiotic-loaded cement;
- Extended postoperative antibiotic therapy (14-21 days);

C. Patients with high reinfection risk (≤2 points):

- Second-stage postponement until laboratory parameter normalization;
- If surgery is necessary – use of hinged constructs;
- Prolonged intensive antibiotic therapy (≥3 weeks).

Results. The mean follow-up period after second-stage reimplantation was 24 months (range: 12-60 months). Successful infection eradication was achieved in 34 patients (85%). Three patients (7.5%) experienced reinfection after the second stage, requiring additional interventions.

Functional outcomes significantly improved after completion of two-stage revision arthroplasty, with KSS functional component increasing from 35.7±9.2 to 72.1±13.5 ($p<0.001$), and OKS from 18.3±5.6 to 34.2±8.9 ($p<0.001$).

Predictors of successful infection eradication. Univariate analysis showed that the following factors were statistically significantly associated with successful infection eradication: 1) CRP level normalization before second stage (OR = 7.8; 95% CI: 2.3-26.5; $p = 0.001$). 2) ESR level normaliza-

tion before second stage (OR = 5.2; 95% CI: 1.7-16.1; p = 0.004). 3) Absence of pathogens in synovial fluid before second stage (OR = 11.3; 95% CI: 3.4-37.8; p < 0.001). 4) Spacer period duration >12 weeks (OR = 4.6; 95% CI: 1.3-16.2; p = 0.018). 5) Absence of MRSA infection (OR = 3.9; 95% CI: 1.2-12.6; p = 0.023). 6) Absence of sinus tract (OR = 3.2; 95% CI: 1.1-9.5; p = 0.031). 7) Proper spacer position on radiography (OR = 2.5; 95% CI: 0.9-7.2; p=0.048)*.

In multivariate analysis, independent predictors of successful infection eradication remained: 1) Absence of pathogens in synovial fluid before second stage (OR=8.7; 95% CI: 2.5-30.3; p<0.001). 2) CRP level normalization before second stage (OR=5.1; 95% CI: 1.4-18.7; p=0.013). 3) Spacer period duration >12 weeks (OR=3.8; 95% CI: 1.1-13.4; p=0.039). 4) Absence of sinus tract (OR=2.9; 95% CI: 1.0-8.7; p=0.042)*.

Multicollinearity analysis showed no significant correlations between predictors included in the model (VIF<2.5 for all variables).

* *Note: This factor has borderline statistical significance as the lower confidence interval boundary includes 1.0.*

Complications. The overall complication rate was 27.5% (11 patients). The most frequent complications were: 1) Extension/flexion mechanism dysfunction – 4 patients (10%). 2) Excessive pain syndrome – 3 patients (7.5%). 3) Complicated wound healing – 3 patients (7.5%). 4) Periprosthetic fracture - 1 patient (2.5%).

Three patients experienced a combination of two complications, explaining the total complication count (11) in 40 patients. The most significant complication requiring repeat surgical intervention was periprosthetic fracture. Extension/flexion mechanism dysfunction was the most common complication.

Prediction system validation. To verify the effectiveness of the developed prediction system, a retrospective analysis of treatment outcomes was performed (Table 4):

Table 4. Prediction accuracy using the developed system

Prognostic Group	Number of patients	Predicted successful cases	Actual successful cases	Prediction accuracy
Low risk (≥6 points)	22	21 (95.5%)	22 (100%)	95.5%
Moderate risk (3-5 points)	12	10 (83.3%)	11 (91.7%)	91.7%
High risk (≤2 points)	6	3 (50%)	4 (66.7%)	75%
Overall	40	34 (85%)	37 (92.5%)	90%

Discussion

Two-stage revision arthroplasty achieved 85% infection eradication success, confirming its effectiveness as the gold standard for chronic PJI treatment.

CRP normalization and negative synovial fluid cultures before reimplantation were key success predictors, consistent with literature (Klemt et al., 2023; Ascione et al., 2024). However, CRP may remain elevated in patients with inflammatory comorbidities (Pope & Choy 2021; Johri et al., 2023). Spacer periods >12 weeks showed better outcomes, aligning with ICM consensus recommendations.

Sinus tract presence emerged as an independent reinfection risk factor. Staphylococcus aureus predominated (30%), with MRSA cases showing worse outcomes (Kim et al., 2022; Kraus et al., 2024). Main PJI causes were glucocorticosteroid injections and trauma (15% each).

The developed scoring system achieved 90% prediction accuracy for second-stage outcomes. Differential surgical approach based on risk stratification yielded better functional results: low-risk patients (KSS 78.4±10.2) versus high-risk patients (KSS 58.9±15.6, p<0.01).

Recommended differential approach:

- Low risk (≥6 points): standard protocol, 12-16 weeks spacer
- Moderate risk (3-5 points): extended spacer (16-20 weeks), enhanced stability implants
- High risk (≤ 2 points): spacer >20 weeks, hinged constructs, prolonged antibiotics.

Study limitations include retrospective design, small sample size, non-standardized protocols, and short follow-up.

Conclusions

Based on the research findings: two-stage arthroplasty achieved 85% infection eradication success; CRP/ESR normalization and negative cultures reliably predict success; optimal spacer duration ≥12 weeks, especially for complex infections; Sinus tract, MRSA, and short spacer duration are reinfection risk factors; scoring system enables 90% accurate risk stratification; differential approach optimizes outcomes based on reinfection risk; functional improvement occurs but remains inferior to primary arthroplasty; prospective validation studies needed.

ექსპერიმენტული მედიცინა

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(წარმოდგენილია აკადემიის წევრის რ. ხეცურიანის მიერ)

პერიპროთეზული სახსრის ინფექცია (პსი) მუხლის ართროპლასტიკის გართულებაა, რომლის შემთხვევაშიც, მეორე ეტაპის რევიზიის დროის განსაზღვრის კრიტერიუმები სადავოა. ქირურგიული მკურნალობის შერჩევისა და წარმატებული რეიმპლანტაციის პროგნოზირებადი ფაქტორების გამოსავლენად, შემუშავებულ იქნა დიფერენცირებული მიდგომა. პსი-თვის (2014–2024 წწ.) ართროპლასტიკური მუხლის სახსრის რევიზიის ორეტაპგამოვლილი 40 პაციენტის რეტროსპექტული ანალიზით შეფასდა ლაბორატორიული, მიკრობიოლოგიური, რადიოლოგიური და ფუნქციური პარამეტრები. კვლევით დადგინდა, რომ გამოკვლეულ პაციენტთა 85%-ში ინფექცია წარმატებულად იქნა ელიმინირებული. მეორე ეტაპის შედეგების პროგნოზირებისათვის შემუშავდა შეფასების სისტემა, რომელმაც უზრუნველყო პროგნოზირების 90%-იანი სიზუსტე და გამოავლინა რისკის ჯგუფებს შორის ფუნქციური გაუმჯობესების მნიშვნელოვანი სხვაობები.

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