MICROBIOLOGICAL SPECTRUM OF SSI PATHOGENS IN PATIENTS WITH CHRONIC INFECTIOUS SPONDYLITIS REQUIRING REVISION SURGERY: RESULTS OF CONTINUOUS MONOCENTRIC 5-YEAR MONITORING

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Objective. To analyze the results of the continuous monocentric 5-year microbiological monitoring of causative agents of surgical site infection (SSI) in patients who underwent primary surgery for chronic infectious spondylitis and required revision surgery.
Material and Methods. The study included patient data from 2018 to 2022. The primary cohort included 569 consecutively operated patients with chronic infectious spondylitis of nonspecific ($n_1 = 214$) and tuberculous ($n_2 = 355$) etiology. The analyzed sample was formed taking into according to inclusion and exclusion criteria. Thus, in 99 patients who required revision surgical interventions due to the development of SSI, a continuous microbiological monitoring of pathogens was performed, including the assessment of drug resistance and the timing of the development of infectious complications. Periodization of the time of SSI development was performed according to the accepted classification of Prinz et al. (2020), the assessment of drug resistance spectrum was performed according to the EUCAST recommendations (2020) and taking into account the approved methodological recommendations.
Results. In the general structure of surgical interventions for chronic infectious spondylitis, the share of revision interventions due to the development of SSI was 17.4 %. The highest incidence of complications was noted in the late postoperative period ($\chi^2 = 9.237$; $p = 0.009$). Bacterial detection from the material of vertebral localization was noted in 43 cases (48.3 %), pathogen strains were isolated in urine in 28 (60.8 %), in decubital ulcers in 11 (23.9 %) and in hemoculture in 7 (15.2 %) patients. Culture negative SSI was detected in 10 cases (10.1 %) in the late period. Infectious complications in the setting of chronic non-specific spondylitis were detected more frequently than in spondylitis of tuberculous etiology ($\chi^2 = 21.345$; $p < 0.001$). Gram-positive multidrug-resistant and Gram-negative bacteria with extreme resistance prevailed in the microbiological landscape of late SSI, and Gram-positive strains without drug resistance in that of early and delayed SSI ($\chi^2 = 17.516$; $p = 0.0032$).
Conclusion. Drug-resistant Gram-positive bacteria predominate in the structure of SSI with a significantly higher frequency of complication development. Nonspecific etiology of spondylitis is associated with a significantly higher incidence of SSI. In the absence of a positive result of bacteriological examination of the material of vertebral localization, it is advisable to collect blood, decubital ulcer secretion and urine sampling.

Key Words: surgical site infection, SSI, spondylitis, complications, microbiological monitoring.
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Chronic infectious spondylitis comprises an etiologically heterogeneous group of aggressive lesions united by the predominant destruction of the anterior spinal column [1–3].

The standard for the treatment of acute forms (the duration of the disease is no more than 30 days) of infectious spondylitis includes isolated etiotropic antimicrobial therapy for types A1–B2, according to Pola et al. (2017), or debridement of the infectious process site in combination with extrafocal instrumentation and long-term etiotropic antimicrobial therapy [4]. When spondylitis becames chronic (meaning that the therapeutic pause lasts for three months or longer), not only debridement of the suppurative focus is required, but also a three-column reconstruction with sagittal balance parameter correction as a key criterion for guaranteeing the patient's quality of life during the postoperative period [5]. The performance of such surgeries is associated with high risks of developing a deep surgical site infection (SSI) both in

the early (first 30 days after the surgery) and in the long-term period [6–9]. The progression of the infectious process more often results in the formation of two pathological conditions: segmental instability with the development of pseudoarthrosis and secondary spinal stenosis with neurological conditions [10–12]. Among the main challenges solved during revision surgeries, it is essential to highlight the relief of signs of local and systemic inflammatory response syndrome, the restoration of spinal stability, and the decompression of intracanal neural structures [13–15].

One of the causes for SSI is the high resistance of microbial strains to antimicrobial drugs, which, according to various authors, ranges from 1.1 to 7.4 % [16, 17]. Despite the optimization of the schemes of preoperative systemic antimicrobial therapy and the improvement of methods for the prevention of SSI (intrawound use of vancomycin and irrigation of the surgical area with iodine-containing antiseptic solutions), the incidence of infectious complications after reconstructive surgeries in conditions of chronic infectious spondylitis reaches 21–29 % [18–20].

Monitoring of the microbiological spectrum of SSI pathogens is a major asset to both the prevention of infectious complications of primary reconstructions in chronic spondylitis and the treatment of SSI in patients who require revision surgeries. The lack of specialized articles and the accumulated experience of the institution provide a way to systematize the data on the issue under consideration.

The objective is to analyze the results of the continuous monocentric 5-year microbiological monitoring of causative agents of surgical site infection (SSI) in patients who underwent primary surgery for chronic infectious spondylitis and required revision surgeries.

Answers to the following questions are required:

1) Are there differences in the microbial landscape depending on the timing of SSI development?

2) What is the structure of drug resistance of pathogens depending on the time of SSI development?

Design: continuous multicenter cohort study corresponding to Class III, according to Burns et al. (2011).

Material and Methods

The study was performed from January 1, 2018 to December 31, 2022.

The inclusion of patients in the study was performed considering the following criteria:

- chronic spondylitis etiologically verified by histological or bacteriological technique at the time of primary reconstructive surgery;
- the presence of SSI requiring revision surgery;
- patient's age 18 years and more at the time of revision surgery;
- verification of wound cavity discharge with determination of the spectrum of drug sensitivity of the SSI pathogen;
- verification of the pathogen from hemoculture (triplicate blood sampling at the height of fever), urine, subclavian catheters, and superficial discharge of decubitus ulcers in culture-negative SSI, combined with the presence of clinical manifestations;
- follow-up for a period of 6 months or more.

Exclusion criteria: no indications for revision surgery.

During the analyzed period, 569 patients with chronic infectious spondylitis were sequentially operated on: primary reconstructions were performed in 364 (63.9 %) cases, and revision surgeries were performed in 205 (36.1 %) cases (primary surgeries were performed outside the institution). The final cohort consisted of 99 patients who suffered SSI at different times of the postoperative period, requiring repeated surgery. The study flow diagram is shown in Fig.

The following parameters are distinguished in the structure of the analyzed parameters: 1) a variant of the SSI pathogen; 2) the spectrum of drug resistance of SSI pathogens; 3) the period of development of SSI according to the periodization according to Prinz et al. (early: ⩽6 weeks; delayed: >6 weeks; late: >12 months) [21].

The sampling of organic matter for bacteriological examination was performed before the revision surgery from the wound exudate (in the presence of a fistula) and directly during the intervention (granulation tissue, pus). In cases of delayed and late SSI and instability of the posterior instrumentation, the removing of supporting elements was attended by ultrasound treatment of the implant surface, followed by bacteriological examination.

The detection of non-specific microflora and *Mycobacterium spp*. was performed via inoculation onto a solid and liquid medium. DNA detection of the *Mycobacterium tuberculosis-complex* and amplification of the nucleotide sequence of IS6110, a marker of the Mycobacterium tuberculosis complex, were performed using the test system of DNA-Technology Scientific production association (Russia) by real-time PCR (RT-PCR) on an iCyclerQ analyzer from Bio-Rad (USA).

The threshold value of the colony-forming unit (CFU) of SSI pathogens for inclusion in the study was taken to be $\geqslant 10^5$ (a lower CFU value was considered a variant of contamination of the sample).

Bacteriological examination of biomaterial for anaerobic and facultative anaerobic organisms in all cases was supplemented by the detection of drug susceptibility of SSI pathogens by the disk diffusion test according to the guidelines of EUCAST (2020) and in accordance with the standards and guidelines of procedural guidelines MUK 4.2.1890–04 "Determination of antimicrobial drug susceptibility of organisms", approved by the Public Health Officer of the Russian Federation on March 4, 2004. The verification for low-pathogenic microflora was not performed due to a lack of technical capacity.

In accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and the USA Food and Drug Administration

(FDA), the microorganisms with multidrug resistance (resistance to one antimicrobial drug in three or more groups of drugs), extensively drug resistance (resistance to one or more antimicrobial drug in all groups, with the exception of 1–2 categories) and pandrug resistance (resistance to all antimicrobial drugs in all groups) were isolated in the structure of drug susceptibility [22].

A histopathological examination was performed on the basis of studying the specimen of vertebral localization obtained by needle core biopsy.

The statistical analysis was performed in accordance with the recommendations of the International Association for Osteosynthesis [23]. We used the Statistical Package for the Social Sciences (SPSS) software, version 22.0 (SPSS Inc., Chicago, IL, USA). The test of the studied parameters for the normality of the distribution was performed according to the Kolmogorov-Smirnov test. The bilateral significance value for all quantitative parameters was $p < 0.05$, that suggests their abnormal distribution. The Kruskal-Wallis H-test was used to evaluate the significance of the differences in the timing of SSI development. The effect of the spondylitis etiology on the spectrum of drug susceptibility was tested according to Pearson's chi-squared test with the construction of contingency tables. The differences were considered statistically significant if the bilateral p 0.05.

Results

According to the periodization of the SSI development by Prinz and Vajkoczy [21], the highest rate of complications was noted in the late postoperative period: 54 (54.5%) cases; there were fewer cases in the early (31 patients) and delayed (14 patients) periods (2 = 9.237; p = 0.009).

The SSI pathogens were verified in 89 (89.8 %) patients, while the detection of microorganisms from the vertebral localization specimen was noted in 43 (48.3 %) cases. In cases of *culture-negative* SSI combined with clinical manifestations (fistula in the surgical site, increased CRP > 10 mg/l, and ESR > 30 mm/h) and histologic signs of inflammation, strains of pathogens were isolated in urine in 28 (60.8 %), in decubital ulcers in 11 (23.9 %) and in hemoculture in 7 (15.2 %) patients.

In 10 (10.1 %) patients with clinical signs of SSI, histologic signs of inflammation and a negative result of bacteriological examination of the specimen of both vertebral and other localization, the diagnosis of "SSI with an unidentified pathogen" was established. Meanwhile, the infection was detected in the late postoperative period in all cases.

The etiology of chronic spondylitis had a considerable effect on the incidence rate of SSI: postoperative complications associated with chronic nonspecific spondylitis were observed in 67 (67.6 %) cases and in 32 (32.3 %) in tuberculous cases; $\chi^2 = 21.345$; $p < 0.001$.

Significant differences have been revealed in the structure of the microbial landscape. For example, multidrug-resistant gram-positive and gram-negative bacteria with extensively drug resistance were more often isolated in patients with late SSI, while the pathogens of early and delayed SSI were more often gram-positive bacteria without drug resistance ($\chi^2 = 17.516$; $p = 0.0032$). Verification of two microorganisms was noted in 32 observations, three in 6 observations.

The distribution of selected isolates of vertebral localization, depending on the timing of SSI development, is given in the Table.

During the evaluation of drug resistance of pathogens obtained from vertebral localization, the proportion of gram-positive multidrug-resistant strains was 30.3 %, 63.0 % of which accounted for *Staph. Epidermidis* (MRSE) and 37.0 % for *Staph. Aureus* (MRSA). In the structure of gram-negative bacteria, the proportion of resistant strains reached 80.0 %: 87.5 % of the isolates had extensively drug resistance (*Klebsiella spp.* and *Acinetobacter spp.*) and 12.5 % had pandrug resistance (*Pseud. Aureginosa*).

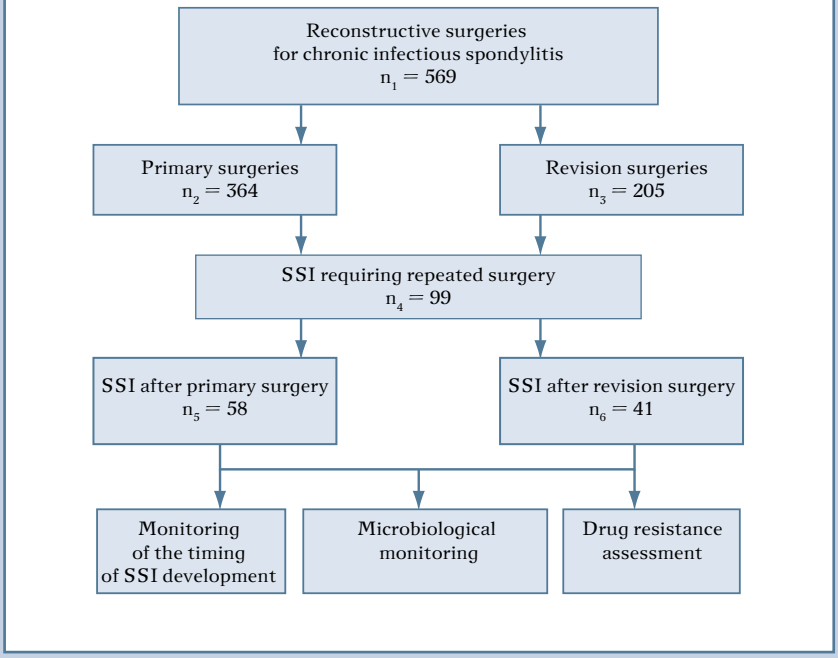

Fig.
Study flow diagram: SSI – surgical site infection

Table
Microbiological landscape depending on the timing of development of surgical site infection (SSI), n (%)

Strains	Total	Early SSI	Delayed SSI	Late SSI
Gramm-positive	33 (76.7)	8 (18.6)	4 (9.3)	11 (25.5)
Including multidrug-resistant	10 (30.3)	1 (2.3)	1 (2.3)	8 (18.6)
Gramm-negative	10 (23.2)	2 (20.0)	1 (10.0)	–
Including extensively drug-resistant	6 (60.0)	1 (10.0)	1 (10.0)	4 (40.0)
Pandrug-resistant	1 (10.0)	–	–	1 (10.0)

* statistically significant differences were detected between the late and early/delayed SSI groups according to the Kruskal – Wallis H test ($\chi^2 = 17{,}516$; $p = 0{,}0032$).

Discussion

Revision surgeries for spondylitis are one of the most difficult issues in spine surgery since they are associated with a large number of infectious complications and high economic expenditures for providing secondary care [24, 25]. Despite the increased number of publications in the considered field, data on the long-term outcomes of revision surgery in patients with chronic infectious spondylitis is limited, and data reflecting the results of microbiological monitoring in this cohort are given in single articles [1, 4, 6, 9].

The prediction of SSI development in spine surgery remains relevant, although there is no consensus. Among the risk factors, there are patient-associated (Charlson index, BMI, concomitant rheumatological pathology and others) and surgery-associated (primary or revision surgery, duration of surgery and blood loss volume, surgery level, and others) [18, 19, 24]. Mueller et al. [7] proposed a risk scale for the development of SSI after spine surgery, in which the revision nature of the intervention is considered one of the most significant predictors of infectious complications [7].

The study of long-term outcomes in patients operated on for nonspecific spondylodiscitis shows a significant dependence between the type of pathogen and mortality. According to Kehrer et al. [25], mortality in the early and delayed postoperative periods is higher in patients with multidrug-resistant strains of *Staph. aureus*, while multidrug-resistant gram-negative microorganisms were more often detected in the late period. Similar outcomes were found in our cohort: there was one lethal outcome of a patient with late deep SSI associated with gram-negative extensively drug-resistant bacteria.

One of the ways to prevent SSI during initially pathogen-free spine surgery is the intrawound administration of vancomycin. A meta-analysis by Shan et al. [26] indicates a significant effect of this technique on the risk of infectious complications. Attention should also be paid to the nature of microorganisms in the presented cohort associated with SSI in the early postoperative period: gram-positive bacteria were detected in 75 % of cases, which provides a recommendation for the intrawound administration of vancomycin in this category of patients.

Gram-positive microorganisms were the main strains in the general cohort of SSI pathogens: 76.7 % versus 23.2 %, with *Staphylococcus spp*. on the leading position. Representatives of *Enterococcus spp*., mainly *E. faecalis* and *E. faecium*, were detected in the structure of the hospital-acquired flora, while the pathogen was detected in urine and decubital ulcers secretion. A feature of this group of microorganisms was multidrug resistance to third- and fourth-generation fluoroquinolones. Similar trends were detected during 6-year monitoring of the structure and resistance of the leading pathogens at the Russian Scientific Research Institute of Traumatology and Orthopedics, named after R.R. Vreden [27].

Conclusion

Microbiological monitoring in patients with chronic infectious spondylitis has identified the following: gram-positive drug-resistant bacteria predominate in the structure of SSI pathogens; the development of late SSI is statistically significant due to multidrug-resistant gram-positive and extensively drug-resistant gram-negative microorganisms; the nonspecific etiology of spondylitis is associated with a considerably higher incidence rate of SSI; if there is no positive outcome of bacteriological examination of the vertebral localization specimen, it is advisable to take blood, discharge from decubital ulcers and urine.

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The study was approved by the local ethics committees of the institutions. All authors contributed significantly to the research and preparation of the article, read and approved the final version before publication.

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