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Etiology of infectious spondylodiscitis: is there an associaton with successful treatment?

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Abstract

Introduction Infectious spondylodiscitis is rising in incidence and and is often a late diagnosis and identification of the causative agent.

The **objective** was to evaluate the treatment outcomes of patients with infectious spondylodiscitis depending on the positive/negative results of intraoperative microbiological culture.

Material and methods Treatment outcomes of 52 patients with infectious spondylodiscitis were retrospectively analyzed with no culture growth in the biological samples (group I, $n = 22$) and with identified pathogen (group II, $n = 30$). The diagnosis was verified using MRI imaging, intraoperative microbiological culture test, the clinical picture and blood inflammation markers (ESR and CRP). Poor outcomes were associated with death and/or recurrent spondylodiscitis.

Results Positive culture growth was detected in 57.7 % with staphylococci predominated in 57.2 % and *Staphylococcus aureus* detected in 42.9 %. Patients of group I were twice as likely to take antibiotics at the preadmission stage ($p = 0.0049$), had a 20 % longer delay in diagnosis ($p = 0.7286$), and had lower CRP and ESR levels than those in Group II ($p > 0.05$). Adverse events included one fatal case in each of the groups; recurrent infections occurred in 13.3 % of cases of group II ($p = 0.3814$) with three quarters of cases caused by *Pseudomonas aeruginosa*.

Discussion Poor prognostic factors in infectious spondylodiscitis include negative microbiological results, neurological impairment and concomitant endocarditis ($p \leqslant 0.05$). *S. aureus* associated spondylodiscitis is accompanied by increased mortality and morbidity. Patients with spondylodiscitis with a negative microbiological test result compared with patients with a culture-positive infection, had a better treatment outcome with minimum recurrent rate ($p > 0.05$).

Conclusion Spondylodiscites with a negative microbiological result compared with a culture-positive infection had a better treatment outcome with a minimum of relapses ($p > 0.05$).

Keywords: infectious spondylodiscitis, etiology of spondylodiscitis, spinal infection, causative agent of spondylodiscitis, recurrent spinal infection, outcomes of spondylodiscitis, antibiotic therapy

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INTRODUCTION

The problem of treating patients with infectious diseases of the spine (spondylodiscitis) has currently become increasingly relevant due to the increasing incidence of the pathology. The incidence of infectious spondylodiscitis (IS) in France for 2002–2003 was 0.2–2.4 per 100,000 population per year [1], increasing to 6.1 by 2010 and to 11.3 in 2019 [2]. According to the German registry, the annual incidence of IS in 2020 was 14.4 per 100,000 population per year [3].

Difficulty of diagnosis and low frequency of detection of the etiologic factor are other problems of infectious diseases of the spine. According to the French SPONDIMMO study, the median duration of symptoms before the diagnosis of IS is 25 (0–427) days [4]. By the time of diagnosis, outpatients are taking both nonsteroidal anti-inflammatory and antibacterial drugs, which may ultimately affect the detection of infectious agents.

The absence of microbial growth in biological material samples can reach 68 % [5]. Pola et al. reported negative microbiological culture as a statistically confirmed negative prognostic factor IS [6]. However, there is a paucity of studies that could provide or compare treatment outcomes of IS with the pathogen being detected or undetected.

Based on data from the Federal Trauma and Orthopedic Center, we undertook to review the treatment outcomes of patients with infectious spondylodiscitis depending on the results of microbiological examination of intraoperative culture.

The **objective** was to evaluate the treatment outcomes of patients with infectious spondylodiscitis depending on the positive/negative results of intraoperative microbiological culture.

MATERIAL AND METHODS

A continuous retrospective analysis of outcomes of patients with infectious spondylodiscitis was conducted at the Federal Center for Trauma, Orthopedics and Joint Replacement (Cheboksary, hereinafter referred to as the Center) between 2016 and 2022.

The study included all cases of conservative and surgical treatment of IS, with the exception of patients aged 18 years and younger (n = 52). The diagnosis of IS was based on clinical findings, MRI, blood inflammation markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)), the results of microbiological examination of intraoperative tissue biopsies and swabs from removed metal constructs. The delivery time of the biomaterial to the laboratory was 15–60 minutes.

The scoring system for spondylodiscitis termed SponDT (Spondylodiscitis Diagnosis and Treatment) based on the inflammatory marker C-reactive protein (CRP), the VAS scale of pain and magnetic resonance imaging (MRI) was used to monitor progression of the disease [7].

Blood sterility tests were performed in patients with signs of a systemic inflammatory reaction (increased blood procalcitonin levels of more than 1.0 ng/ml) who did not receive antibacterial therapy (n = 2).

Examinations included biopsy material (n = 4), intraoperative tissue biopsies (n = 48), swabs from removed metal constructs (n = 14). Biological material was taken from patients receiving conservative therapy in the operating room using needle aspiration from the disc space and the X-ray image intensifier.

Intraoperative tissue biopsy samples were collected in a quantity of at least three, followed by isolation of microorganisms in accordance with approved standards of microbiological research. Tissue samples were homogenized and then placed in thioglycollate broth. Subculture was performed on dense nutrient media using Columbia, Chocolate and Schaedler agars for 1 day; Chocolate and Schaedler agars for 5 days and Schaedler agar for 10 days. Incubation using gas-generating bags was produced for aerobic, anaerobic and capnophilic microorganisms.

Metal constructs removed during surgery were processed in a BRANSON 8510 ultrasound machine (USA) for 5 min at a frequency of (40 ± 2) kHz to isolate microorganisms from microbial biofilms, followed by seeding of the swabs onto nutrient media and onto analyzer vials. The incubation period was 14 days.

Species identification of pathogens with determination of susceptibility was performed using a Vitec 2-compact automatic analyzer (Bio Merieux, France) and a Multiscan FC semi-automatic analyzer (Thermo Fisher, USA).

Patients with IS were divided into two groups: treatment group I (n = 22), with no culture growth in the biological samples; control group II (n = 30), with culture growth obtained. The groups were comparable by gender, age, BMI and comorbidity (Table 1).

Table 1

Characteristics of patients in the study groups

Description	Group I (n = 22)		Group II (n = 30)		p < 0.05
	abs.	%	abs.	%	
Male	12	54.5	16	53.3	1.0000
Female	10	45.5	14	46.7	
Comorbidities including:					
diabetes mellitus	4	18.2	7	23.3	0.7411
oncopathology	1	4.5	2	6.7	1.0000
HIV	0	0.0	2	6.7	0.5023
systemic diseases	2	9.1	2	6.7	1.0000
Localization of the infectious process in the spine, incl.:					
cervical	3	13.6	1	3.3	0.3053
thoracic	5	22.7	6	20.0	1.0000
lumbar or lumbosacral	14	63.6	23	76.7	0.3625
Scoring system for spondylodiscitis (SponDT):					
mild	0	0.0	1	3.3	1.0000
moderate	10	45.5	15	50.0	0.7852
severe	12	54.5	14	46.7	0.7793
The route of infection:					
primary (hematogenous)	14	63.6	23	76.7	0.1461
secondary (postoperative)	8	36.4	7	23.3	
Number of outpatients treated with antibiotics	19	86.4	13	43.3	0.0049*
Age, years	56.8 (50.2–60.8)		57.8 (56.4–64.6)		0.7564
BMI, kg/m^2	26.3 (23.2–29.4)		28.2 (26.1–30.4)		0.2977
Period from onset of disease to diagnosis, days	122.5 (64.3–180.7)		99.9 (64.9–134.3)		0.7286

* — statistically significant differences

Pain was assessed after surgery and at the follow-up using the visual analogue scale VAS, satisfaction with treatment results was evaluated using the EQ-5D and EQ VAS questionnaires [8, 9].

Complete healing of the postoperative wound and normal laboratory and radiological findings at the time of the study (even with persistent neurological deficit and/or chronic pain syndrome) were rated as favorable outcomes. Death and/or recurrence of spondylodiscitis with clinical and instrumentation signs of infection was rated as a poor outcome. The total observation period after debridement was 32.9 (24.9–35.1) months.

The data were recorded in the form of spreadsheets; visualization of the data structure and the analysis were produced using the MS Office Excel, 2007 (Microsoft, USA) and the Graf Pad software. For quantification, a test for the normality of distribution was performed using the Kolmogorov – Smirnov criterion. The mean value and standard deviation with 95 % CI were used to describe parameters in case of normal distribution. Comparison of quantitative characteristics between comparison groups was performed using the Mann – Whitney criterion. Categorical data (gender, outcome) were described by conditional codes of unmeasured categories that were not subject to ordering. Fisher's exact test was used to assess the effectiveness of the treatment in the groups. Differences in indicators between the groups were considered statistically significant at $p < 0.05$.

RESULTS

No growth of microorganisms in the intraoperative biological cultures ($n = 21$) and tissues during biopsy ($n = 1$) was observed in 42.3 % ($n = 22$) from 52 patients treated for IS. Patients with negative culture results (group I) received antibacterial therapy at the prehospital stage ($p = 0.0049$) more often as compared with group II and had a 20 % longer delay in diagnosis ($p = 0.7286$). The majority of patients in both groups suffered from lesions of the lumbar or lumbosacral spine. Although no statistically significant differences in the severity of spondylodiscitis were found in the observation groups severe spondylodiscitis was more common among patients of Group I (54.5 % versus 46.7 %).

Two cases of IS (6.7 %) with isolated microorganisms were classified as polymicrobial infections and were represented by microbial associations:

1) *Pseudomonas aeruginosa* + *Enterococcus faecalis* + *Enterococcus faecium* + *Staphylococcus epidermidis MRSE*;
2) *Staphylococcus epidermidis MRSE* + *Corynebacterium*.

Staphylococci (57.2 %) were the leading pathogens among the causative agents of monomicrobial infection (93.3 % of cases) with *Staphylococcus aureus* predominating. The second frequent occurrence was gram-negative microorganisms (21.4 %), represented by *Escherichia coli, Pseudomonas aeruginosa* and *Klebsiella pneumonia* (Fig. 1).

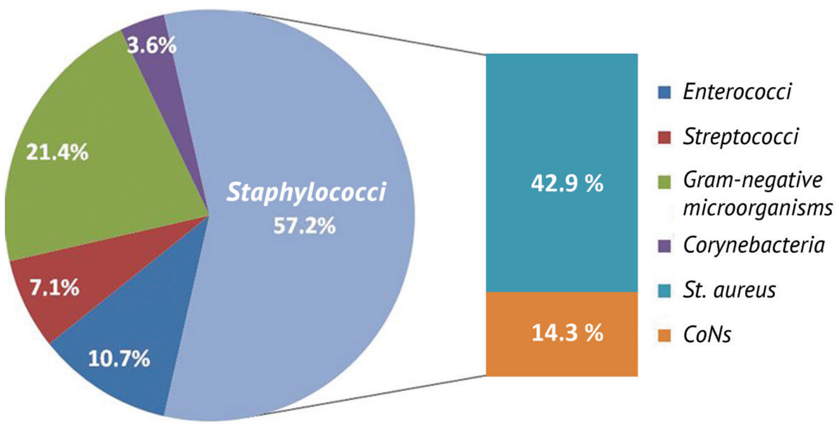

Fig. 1 Spectrum of spondylodiscitis pathogens with one isolated microorganism

A blood test for sterility showed a positive result in two control patients who received no antibacterial therapy at the outpatient stage: *Staphylococcus aureus* was detected in one case and *Streptococcus pneumoniae* was isolated in the other case. Inflammation blood test levels the were elevated in both observation groups at the prehospital stage, with a predominance of higher values of ESR, CRP and D-dimer seen in group II without statistically significant differences (Table 2).

Table 2

Blood test measurements in the groups prior to debridement

Description	Group I (*n* = 22)	Group II (*n* = 30)	$p < 0.05$
Blood WBC, 10^9/L	8.3 (7.0–9.5)	7.7 (6.6–8.9)	0.3152
ESR (mm/h)	35.1 (20.7–49.6)	52.9 (13.7–66.1)	0.0597
CRP (mg/L)	52.9 (14.4–83.8)	61.1 (42.3–80.0)	0.1802
D-dimer (ng/ml)	1137.9 (643.6–1632.0)	1305.9 (880.2–1732.0)	0.5104

MRI images indicated an abscess of various localizations detected in 54.5 % (*n* = 12) in group I and in 43.3 % (*n* = 13) of cases in group II ($p = 1.0000$). Conservative therapy included antibiotics (6–12 weeks) and spine fixation with a rigid corset and performed for one patient in group I and three patients in group II ($p = 0.6288$). The remaining patients with IS underwent surgical treatment (Table 3).

Table 3

Methods of surgical debridement in groups

Surgical interventions	Group I (*n* = 21)		Group II (*n* = 27)	
	abs.	%	abs.	%
Decompression with staged anterior and dorsal spondylodesis	2	9.5	–	
Anterior spondylodesis	2	9.5	2	7.4
Anterior fusion with plate fixation	2	9.5	–	
Posterior spondylodesis with TPF fixation	14	66.7	21	77.8
Debridement with decompression only	1	4.8	3	11.1
Posterior spondylodesis with autologous bone chips	–		1	3.7

The average duration of intravenous antibiotic therapy was (12.4 ± 3.8) days and (71.9 ± 55.4) days of oral antibacterial therapy. Empirical intravenous antibacterial therapy "glycopeptide + beta-lactam" was the most common intravenous regimen (54.5 %) in group II followed by the combination of "cefuroxime + amikacin" (22.7 %); monotherapy with third- and fourth-generation cephalosporins (13.6 %) and combination of cephalosporins with rifampicin (9.1 %). Fluoroquinolones combined with rifampin were the most common regimen of empirical oral antibacterial therapy (36.4 %); monotherapy with quinolones (18.2 %) or clindamycin (18.2 %), the combination of quinolone + doxycycline (13.6 %) or quinolone + co-trimoxazole (13.6 %) were other common oral regimens. Oral combination therapy with two or more antibiotics was used in 48.1 % of cases. In case of successful sanitation, no reliable differences in the quality of life of patients in the observation groups were found (Table 4). Patients were satisfied with the quality of life scored 75 on average.

Table 4

Patient satisfaction with the treatment performed at the follow-up stage

Description	Group I (*n* = 22)	Group II (*n* = 30)	$p < 0.05$
Assessment of quality of life using the EQ-5D questionnaire (scored from 0 to 1)	0.71 (0.61–0.80)	0.76 (0.67–0.86)	0.3083
Health assessment using the EQ-VAS “health thermometer” (scored from 0 to 100)	70.33 (59.23–81.43)	76.83 (69.83–84.14)	0.3256
VAS score	2.53 (1.58–3.49)	2.11 (1.43–2.80)	0.6184

The average observation period after debridement was 31.5 months (20.5–36.5) in group I and 34.0 months (23.0–37.0) in group II, $p = 0.6397$. Relapses in the form of deep spinal infection were not detected in group I, relapses were observed in 4 (13.3 %) patients in group II and debridement was performed surgically ($p = 0.3814$). There was one fatal outcome in each observation group: due to tumor progression in group I and after conservative treatment of recurrent infectious spondylodiscitis due to mesenteric artery thrombosis in group II. Recurrent infections were observed in three out of four cases of spondylodiscitis caused by *Pseudomonas aeruginosa*.

DISCUSSION

Microbiological examination is a key element in the diagnosis and treatment of IS. However, it is not always possible to obtain cultural growth when examining biological material. The authors of several large prospective studies found that the pathogen could not be isolated in 21–34 % of cases [1, 10–12].

Stangenberg et al. reported the detection rate of bacterial pathogens through intraoperative sampling being 66.3 % and could be increased by the results of the blood cultures to a total of 80.6 % (n = 170/211) [13]. Pola et al. reported a microbiological diagnosis established in 74.3 % of cases; observed sensitivities of blood culture, CT-guided biopsy and surgical biopsy were, respectively, 55.5, 44.1 and 59.6 % [6]. Our results of searching for the causative agent of IS differ from those reported by our foreign colleagues, since we limited ourselves to microbiological examination of CT-guided biopsy and surgical biopsy, obtaining a positive result in 57.7 % of cases. The fact that 61.5 % of patients received antibacterial therapy preoperatively, sterility blood testing was not produced for them. The test as part of the screening diagnosis of IS could have clarified our results in the search for the infectious agent.

Assessing the structure of the pathogens isolated during the microbiological study, we obtained results similar to those of other studies, with *S. aureus* being the most common pathogen isolated in approximately 50 % of cases of spondylodiscitis [14, 15]. However, the incidence of spondylodiscitis in Germany reviewed over a ten-year period published in 2023 presented data indicating a decrease in the proportion of *S. aureus* in the overall microbial composition: coagulase-negative staphylococci were recorded in the majority of cases (27.1 %), followed by gram-negative bacteria (22.4 %), with *S. aureus* accounting for only 19. % [3].

A recent analysis of IS after implantation of metal constructs [16] showed that *S. epidermidis* was the most common pathogen (40.6 %) and has recently become prevalent in patients with implant-associated infection [17]. The growing importance of gram-negative pathogens in the etiology of IS is also evidenced by a study conducted in France in 2010–2019, with the frequency of isolation of the pathogens being 26.4 % (second place after staphylococci, 52.3 %) [2].

IS is a complex condition to treat and is caused by a wide range of organisms [18]. Searching for the causative agent of the infection is an important component of the treatment of patients with IS. According to our data, gram-negative microorganisms and coagulase-negative staphylococci are among the top three with an incidence rate of 21.4 % and 14.6 %, respectively. The trend of increasing gram-negative pathogens and coagulase-negative staphylococci can be associated with epidemiological problems caused by the aging population, an increased number of weakened patients with multiple comorbidities and an increase in invasive procedures and surgical interventions on the spine.

Despite the fact that control patients received etiotropic antibacterial therapy, the best treatment results, characterized by the absence of recurrent infection with similar indicators of satisfaction with the quality of life were obtained in the group with a negative bacteriological study. Data similar to ours were reported by Gillard et al. who described favorable outcomes under empirical two-drug antimicrobial therapy including a fluoroquinolone given by the intravenous route, with no relapses or long-term recurrences versus controls with an established infectious agent and selected etiotropic therapy [19].

Stangenberg et al. reported S. aureus-associated spondylodiscitis being associated with an increased mortality and a higher complication rate with the pathogen due to the high frequency of detection in intraoperative specimens and in blood culture [13]. In contrast to the previously discussed works, Hopkinson et al. emphasized the importance of searching for the causative agent of IS (since the treatment outcome is worse if the causative agent is not detected) and showed a tendency for longer courses of antibiotic therapy. The authors also pointed out that these cases were more difficult to treat. The group of patients was represented by a small sample: 22 cases in the publication of 2021 and 23 in 2016 [21, 22].

In 2018, Pola et al. reported outcomes of 207 cases of IS and concluded that negative microbiological culture was a statistically confirmed negative prognostic factor, along with neurological impairment at diagnosis and underlying endocarditis [6]. Publications of Hopkinson (2001, 2016) and Pola (2018) were descriptive.

In our series, we attempted to analyze the outcome of IS treatment depending on the positive or negative result of intraoperative culture. The worse treatment outcomes of patients with an identified pathogen in our series could be due to undiagnosed bacteremia, since blood sterility testing was not produced for all patients with IS. Interestingly, 75 % of IS recurrent cases were associated with gram-negative pathogens (*Pseudomonas aeruginosa*, in particular), which may indicate an adverse effect of this pathogen on the outcome of IS treatment. Patients in Group I were significantly more likely to use antibiotics at the outpatient stage before culturing, although the optimal solution is to abstain from antibiotics until the microorganism is detected. We hypothesized that taking antibiotics at the outpatient stage increases their total course dose, which could also have a positive effect on the outcome of treatment of IS with a negative microbiological result.

The positive effect on the outcome of treatment of IS correlates with the study by Bhagat et al. who reported that starting antibiotics before detection of the microorganism may help reduce the risk of neurological deficit or spinal deformity [22]. Our study showed that empirical antibiotic therapy "glycopeptide + beta-lactam" used in most cases is no less effective than etiotropic treatment. The limitations of the study are the retrospective nature and small sample. We tested blood for sterility in only two patients, whereas 100 % coverage of this study could have increased the rate of pathogen isolation. The question of a reasonable time balance from the start of antibiotics to the identification of the pathogen remains open.

CONCLUSION

Patients with spondylodiscitis with a negative microbiological test result had a better treatment outcome with a minimum of relapses compared with patients with a culture-positive infection ($p > 0.05$).

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

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