HEMATOGENOUS PYOGENIC VERTEBRAL OSTEOMYELITIS: CLINICAL AND MICROBIOLOGICAL CHARACTERISTICS

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Objective. To analyze clinical picture and composition of pathogens of hematogenous pyogenic vertebral osteomyelitis (PVO) based on the records of a regional clinic admitting patients with this disease.

Material and Methods. A retrospective monocenter analysis of medical records of patients who underwent treatment for hematogenous PVO at the Tyumen Regional Clinical Hospital No. 2 in 2006–2017 was carried out. The nature of the isolated microflora was studied based on 209 inpatient medical records. Out of them, 68 patients were conservatively treated, and 141 were operated on. Ninety three bacterial strains were isolated from the surgical material in 77 patients, 20 strains – from aspiration biopsy in 32 patients, 21 strains – from blood in 20 patients.

Results. The causative agent of PVO was identified in 117 (56.0 %) patients including gram-positive flora in 56.3 % of cases. The main pathogens were *Staphylococcus spp.* (53.8 %). Oxacillin-sensitive *S. aureus* (MSSA) was isolated in 35.5 % of cases, its resistant form (MRSA) in 3.3 %. In 26 (12.4 %) patients, two or more pathogens were detected with a predominance of staphylococcal flora.

Conclusion. The most common cause of hematogenous PVO is gram-positive flora with a predominance of *S. aureus* (38.8 %). Anaerobes were identified in 30.6 % of cases. In 26 (12.4 %) cases, more than one pathogen was isolated. There were no significant differences in the form of the disease with gram-positive and gram-negative flora, and polymicrobial lesions ($p = 0.498$). *S. aureus* is more common in lesions of the cervical spine in comparison with the thoracic ($p = 0.003$) and lumbar ($p = 0.001$) spine. There is a tendency to an increase in peptostreptococci in lesions of the lumbar spine ($p = 0.09$). *S. aureus* is significantly more often isolated in acute in acute form of the disease than in subacute ($p = 0.009$) and chronic ($p = 0.012$) forms, and peptostreptococci – in subacute ($p = 0.001$) and chronic ($p = 0.003$) forms of the disease.

Key Words: hematogenous pyogenic vertebral osteomyelitis, gram-positive flora, *S. aureus*, conservative and surgical treatment.

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Hematogenous pyogenic vertebral osteomyelitis (PVO) is a rare and hardly diagnosed disease. Diagnosis is based not only on radiological findings, but also on the clinical picture, laboratory and microbiological findings [1].

The mean diagnosis time is 2–4 months [2–4]. Annually, 2–4 new cases are diagnosed per 100 000 of the population [5], and morbidity increases with age. The male : female ratio of PVO patients is 5 : 1. The number of new diseased patients increases in the age group of 70–79 years, and reaches the maximum level in patients aged 80 and older [6, 7] and in risk groups (drug-dependent persons and patients with immunodeficiency, including HIV infection). Progressively increasing surgical activity in inpatient departments contributes to dissemination of iatrogenic infection to the spine [8], and adverse effects of nosocomial infections increase steadily [9]. The growth of the absolute number of patients is inevitably accompanied with the increase in the number of complicated forms of disease.

The main pathogen of pyogenic spinal infections is *S. aureus* isolated with the incidence varying from 20.0 to 84.0 % [3, 10–15]. The isolation rate of *S. epidermidis* as the main pathogen of vertebral osteomyelitis varies from 5.0 to 16.0 %, that of *enterobacteriaceae* is 7.0–33.0 %, more often they are associated with genitourinary tract infections and elderly age [10, 12, 13, 15]. Anaerobes are found in 4.0 % of cases and are isolated more often from patients with intraabdominal infections [12, 13]. In the majority of cases, researchers isolate one pathogen of PVO, and polymicrobial etiology occurs in < 10.0 % of patients [13, 14, 16].

It is impossible to isolate a pathogen of vertebral osteomyelitis in 34.3–35.4 % of patients [5, 17]. There may be several reasons for negative findings of bacterial cultures, including antibacterial therapy before biopsy and/or blood sampling, errors in biopsy sampling techniques, and infection process resolution [18].

The main methods to isolate pathogens of vertebral osteomyelitis are biopsy taken from the affected area (closed or open), and blood test for sterility. The general effectiveness of these methods reaches 66.0 %, and an open biopsy

makes it possible to isolate pathogen in 93.0 % of cases [19].

PVO is most commonly an urgent clinical situation, and one of the key factors for treatment is to determine the etiologic factor [8, 20] in order to initiate antibacterial therapy in proper time in combination with orthopedic regime, rigid brace use, and/or surgical aid [3, 20].

Empiric antibacterial therapy for vertebral osteomyelitis should be effective towards the most frequent pathogens of PVO, including *Staphilococcus aureus*, *Enterococcus, Pseudomanas aeruginosa*, and some other microorganisms. If there are signs of sepsis and it is impossible to identify a pathogen, empiric antibacterial therapy can be administered, and this therapy should coincide in time with an attempt to establish an etiologic diagnosis [20].

Parenteral administration of antibiotics is prescribed for at least three weeks, and no dependence has been found between the lengthening of the administration of these drugs for more than six weeks and improving treatment outcomes. In the later period, patients were administered to take tablets. The recommended duration of the additional period of antibacterial therapy varies between six weeks and three months, and depends on individual response to the treatment and pathogen type [6, 8, 21].

Regular monitoring of complete blood count and biochemical blood test findings is obligatory. The main nonspecific parameters reflecting dynamics of inflammatory process are as follows: ESR, CRP, leukocytosis, and a white blood cell count [3, 8].

The objective of the study was to analyze the clinical picture and species composition of pathogens of hematogenous pyogenic vertebral osteomyelitis (PVO) based on the records of a regional clinic admitting patients with this disease.

Material and Methods

A retrospective analysis of 209 medical records of the patients who had undergone treatment for hematogenous pyogenic vertebral osteomyelitis at the Tyumen Regional Clinical Hospital No. 2 in 2006–2017 was carried out. There were 73.2 % (n = 153) of male and 26.8 % (n = 56) of female patients, with the 3 : 1 ratio. The mean age of patients was 50.39 ± 14.00 years. The patients were divided into the following groups: with acute (30.6 %, n = 64), subacute (28.3 %, n = 59), and chronic (41.1 %, n = 86) forms of disease. The disease manifestations were accompanied with febrile fever in 111 (53.1 %) patients, subfebrile fever in 26 (12.4 %) patients, and 72 (34.5 %) patients did not have temperature rise during the prehospital phase.

Sixty-eight (32.5 %) patients were treated conservatively, and 141 (67.5 %) patients were operated on.

We have been using core needle biopsy under radioscopic or CT control as an obligatory diagnostic technique over the last five years. Blood test for sterility was carried out for medical indications.

Microbiological study was carried out for all patients who had been operated on at the lesion area (through the anterior and posterolateral approaches). Sensitivity of the isolated bacteria to antibiotics was estimated by a disk-diffusion method (in accordance with the MUK 4.2.1890-04 before 2015, in accordance with the Clinical Recommendations "Determination of Sensitivity of Microorganisms to Antimicrobial Preparations", Version 2015-02, from 2015 to 2018; and in accordance with the Clinical Recommendations "Determination of Sensitivity of Microorganisms to Antimicrobial Preparations», Version 2018-03, since 2018).

The isolated strains of enterobacteria were studied by double-disk diffusion test for detection of extended spectrum beta-lactamases. Methicillin resistance was determined by disk diffusion method with cefoxitin. The initial patterns of treatment for vertebral osteomyelitis approved for the internal application at the hospital were analyzed.

The statistical analysis was carried out using the IBM SPSS Statistics 21.0 and Statistica 6.0 software packages. The quantitative data are presented as mean deviation and standard error of the mean (M ± SD). Kolmogorov – Smirnov test was used to check the distribution of quantitative attributes.

The data with the normal distribution were compared using Student's t-test for independent samples, and the data with the distribution differing from the normal one were compared using the Mann–Whitney U test. Fisher's exact test and Chi square χ^2 were used to determine differences between qualitative characteristics. Bonferroni correction was used to compare the three groups. Differences in characteristics at the level of $p < 0.05$ were considered to be significant.

Results

All the patients were divided into groups depending on the etiologic factor.

Risk groups, pathogens of diseases, and treatment outcomes of 209 patients with PVO were analyzed. The general characteristics of the patients are listed in Tables 1–3 and Fig.

So, no statistically significant differences in age, sex of patients, forms of disease, diagnosis period, and inpatient treatment duration have been revealed between different etiologic groups.

During the further statistical analysis, the junctional regions of the spine (C7–T1, T12–L1, and L5–S1) were joined with the superposed regions; and no statistically significant differences in distribution by diseased regions of the spine depending on the etiologic factor have been revealed: for the cervical spine $p = 0.349$, for the thoracic $p = 0.809$, and for the lumbar spine $p = 0.918$.

The causative pathogen was identified in 77 samples of bacterial cultures of the surgical material, in 20 samples of biopsy from the lesion area, and in 20 samples from blood test for sterility.

It was possible to identify pathogens in 72.6 % of patients who had undergone surgical interventions at the lesion area due to intraoperative bacterial samples. So, this method could be considered to be the most informative for identification of the etiology of inflammatory lesion of the spine. According to our data, the information value of the core needle biopsy was 62.5 %. The results of

all methods of biological material samplings were summarized, and it was found that the pathogen was isolated in 117 (56.0 %) patients, including 134 positive sampling results. In 26 (12.0 %) patients, more than one pathogen was isolated, and two pathogens isolated from the lesion area were found in 13 (6.2 %) patients.

Gram-negative microorganisms were identified in the lesion area in 56.3 % of cases (n = 68).

The main pathogens were *Staphylococcus spp.* (53.8 %). Oxacillin-sensitive *S. aureus* (MSSA) was isolated in 35.5 % of cases, and its resistant form (MRSA) was isolated in 3.3 %. In 11.6 % of cases, *S. Epidermidis* was isolated from the surgical material. Anaerobes were identified in 30.6 % of cases. The data on the number of pathogens are presented in Tables 4–6.

A. Baumani and *S. aureus* (n = 8) were isolated in three cases from polymicrobial lesions and in acute form of disease (n = 12), including in combination with other species of staphylococci. Chronic form with polymicrobial lesion (n = 9) is also characterized by a predominance of staphylococcal flora. The most interesting are patients with two pathogens isolated from the lesion area. During the surgical debridement of the lesion area, several bacterial samples are taken conventionally, if the inflammatory process propagates outwards the spinal motion segment involving paravertebral abscess and intervertebral disc, or disc and contents of the spinal canal. As a rule, the growth of microorganisms was recorded in different samples taken intraoperatively in the same patient.

The data on the number of affected segments and their localization are as follows: three (1.4 %) patients with monovertebral lesions, 186 (89.0 %) patients with one-segment lesions, 15 (7.2 %) patients with polysegment lesions of two and more segments, and five (2.4 %) patients with multilevel lesions of two and more segments divided by an intact segment.

All the patients with a MRSA-caused disease had admissions to other inpatient facilities in their medical history, before the diagnosing of vertebral osteomyelitis.

In all cases of PVO, initial treatment patterns included prescription of oxacillin (30.0 %), cefazolin (20.0 %), or protected aminopenicillins (50.0 %) with gentamicin or fluoroquinolone. In cases of unknown pathogen, and in the absence of preliminary hospitalization, the initial antibacterial therapy demonstrated a favorable clinical effect. If resistant strains were isolated, the treatment was adjusted depending on microbiological findings. In all cases of MRSA isolated, vancomycin was administered in a dose of 2 g/day, followed with fucidin tablets in 2–3 weeks. All the patients with resistant flora or polymicrobial lesions were consulted by a clinical pharmacologist, and antibiotic therapy was administered on a collegiate basis.

Immobilization of the affected spinal department is obligatory during the conservative treatment, including bed rest in the early period before the pain management, followed with immobilization with a rigid brace. The patients after extrafocal transpedicular fixation or reconstruction and stabilization interventions were activated on the 2nd–5th day after the surgical intervention without external immobilization.

Discusion

Regardless technological advance in methods and tools for diagnostics, vertebral osteomyelitis is still a hard-to-diagnose disease. A mean diagnosis period is 2.6 ± 3.0 months.

Late diagnostics and a short course of antibacterial therapy before the diagnosis specify a stage of the pathological process, when to start specialized treatment. An acute disease onset with the duration up to 4 weeks and accompanied with fever, pronounced pain syndrome, significant increase in inflammatory markers (ESR, CRP, leukocytosis, and shift of band neutrophils in the white blood cell count) results in an acute form of disease. Increase in acute-phase parameters is recorded in 75–98 % of patients at this stage [1]. The subacute form of disease is characterized by less pronounced clinical manifestations within the period of up to three months. In case of the chronic form of disease, laboratory findings reach normal values, pain syndrome is less pronounced, though necrotic and/or proliferative processes predominate in bone tissues. In case of nonradical interventions, abscess drainage without debridement of the focal lesion area often leads to fistula formation.

The main pathogen of hematogenous bone infections is *S. aureus*, and our study proves it. But the share of anaerobic microorganisms in our series is significantly higher than that noted in the majority of the known publications, and it is close to the highest value presented in the literature (29.0 %) [22]. To some extent, the reasons might be as follows: slow growth of staphylococci, prior antibacterial therapy, and possibility to indentify gram-positive anaerobes by microscopy after the culture time established by the Clinical Recommendations.

The share of lesions of the lumbar spine accounts for more than a half of all cases, and the incidence of lesions caused by *Staphilococcus aureus* increases from the lumbar spine to the cervical spine, where it reaches 75 %. The isolation rate of mixed flora is significantly lower; in this case, our findings coincide with the literature data accounting for 11.0 % and 12.4 %, respectively. Two pathogens were isolated from bacterial samples of the surgical material in 13 patients out of 26.

Out of 20 patients with recurrent process, *S. aureus* was identified in 10 cases, including two cases with MRSA. Among patients, who died at the hospital, MRSA was identified in one patient, and MSSA was identified in three patients.

The identification of disease causing pathogen is principal in treatment of inflammatory infections of the vertebral column [20]. The most informative are bacterial cultures of the surgical material in open interventions on anterior structures of the vertebrae. Tests of blood for sterility were carried out in feverish patients and/or in case of a clinical picture of sepsis. Biopsy taken from the lesion area is an effective method and it should be used in a routine way

Table 1
General characteristics of patients with hematogenous pyogenic vertebral osteomyelitis

Parameters	Etiology of disease			p
	gram-positive pathogen	gram-negative pathogen	polymicrobial lesion	
Age, years	50.39 ± 14.00	50.60 ± 15.17	53.04 ± 13.91	0.726
Diagnosis period, months	2.66 ± 2.96	2.65 ± 2.07	2.32 ± 2.69	0.487
Bed days	34.46 ± 17.25	38.50 ± 9.65	43.50 ± 24.60	0.110

Table 2
Distribution of patients by sex, forms of disease, and etiologic factor, n (%)

Parameters	Etiology of disease (pathogen isolated from the lesion area)			p
	gram-positive pathogen	gram-negative pathogen	polymicrobial lesion	
Sex				
Male	41 (71.9)	7 (70.0)	21 (80.8)	0.640
Female	16 (28.1)	3 (30.0)	5 (19.2)	
Forms of disease				
Acute	17 (29.8)	2 (20.0)	12 (46.2)	0.498
Subacute	15 (26.3)	3 (30.0)	4 (15.4)	
Chronic	25 (43.9)	5 (50.0)	10 (38.5)	

Table 3
Distribution of patients by types of surgical intervention, n (%)

Types of intervention	Patients
Anterior debridement of the lesion area (single stage)	32 (22.7)
Debridement combined with instrumented fixation	11 (7.8)
Laminectomy (combined with stabilization in two patients)	3 (2.1)
Resection of the lesion area, anterior spinal fusion	32 (22.7)
Anterior spinal fusion with transpedicular fixation (360° reconstruction)	28 (19.9)
Isolated extrafocal transpedicular fixation	35 (24.8)

at conservative treatment of patients, or at extrafocal instrumented fixation of the spine. In this case, the administration of antibacterial therapy should coincide with the biopsy sampling in time [20]. It is our standard to culture biopsy material for microflora, PCR for DNA of tuberculosis, and histological study. And everything is analyzed by culture-based and molecular genetic methods (standard) [23].

Polymicrobial lesion combined with a high virulence of the pathogen, diabetes mellitus, or immunodeficiency significantly worsens the disease course, increases risk of complications, or treatment failure.

Taking into account the bulk material reflecting the etiology of the disease, the central focus is on the clinical picture and its microbiological characteristics. We plan to present the treatment outcomes in a separate paper.

The duration of the intravenous antibacterial therapy should be at least three weeks with the total duration of the antibacterial therapy of at least six weeks, and up to 12 weeks when medically indicated [6]. A 12-week course of the antibacterial therapy has proved to have no advantages in comparison with a 6-week course [24]. At the same time, the presence of such risk factors of recurrence as chronic dialysis in patients with chronic kidney disease, MRSA isolated from the lesion area, and undrained paravertebral or psoas abscesses, requires to prolong the duration of the antibacterial therapy [25].

Conclusion

The most common cause of hematogenous PVO is gram-positive flora with a predominance of *S. aureus* (38.8 %). Anaerobes were identified in 30.6 % of cases. In 26 (12.4 %) cases, more than one pathogen was isolated.

There were no statistically significant differences in the form of disease (acute, subacute, and chronic) with gram-positive and gram-negative flora, and polymicrobial lesions (p = 0.498).

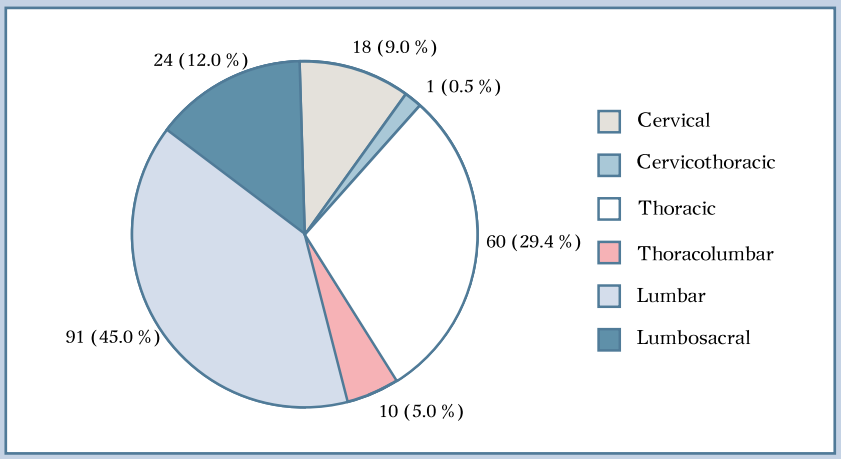

Fig.
Distribution of patients by levels of spinal lesions

S. aureus is more common in lesions of the cervical spine in comparison with that in the thoracic ($p = 0.003$) and lumbar ($p = 0.001$) spine, as well as in the acute form of disease in comparison with subacute ($p = 0.009$) and chronic ($p = 0.012$) forms.

There is a tendency to an increase in peptostreptococci in lesions of the lumbar spine ($p = 0.09$), and this flora is significantly more often isolated in subacute ($p = 0.001$) and chronic ($p = 0.003$) forms of disease.

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Table 4
Pathogens of hematogenous pyogenic vertebral osteomyelitis isolated from the lesion area

Pathogen	Number of strains, n (%)
Gram-positive	68 (56.3)
S. aureus (MSSA)	43 (35.5)
S. aureus (MRSA)	4 (3.3)
S. epidermidis	14 (11.6)
S. saprophiticus	2 (1.7)
S. haemoliticus	2 (1.7)
E. faecium	3 (2.5)
Gram-negative	16 (13.2)
P. aeruginosa	4 (3.3)
E. coli	5 (4.2)
A. baumani	4 (3.3)
K. pneumoniae	1 (0.8)
Pr. mirabilis	1 (0.8)
A. lwoffi	1 (0.8)
Gram-positive anaerobes	28 (23.1)
Peptococcus	1 (0.8)
Peptostreptococcus	22 (18.2)
Clostridium	5 (4.1)
Gram-negative anaerobes	9 (7.4)
Bacteroides	9 (7.4)

Table 5

Distribution of pathogens isolated from the lesion area by localization, n (%)

Pathogen	Affected region of the spine		
	cervical	thoracic	lumbar
*S. aureus (MSSA)**	12 (75.0)	15 (31.9)	16 (27.6)
S. aureus (MRSA)	0 (0.0)	1 (2.1)	3 (5.2)
S. epidermidis	0 (0.0)	5 (9.4)	9 (15.5)
S. saprophiticus	1 (6.3)	0 (0.0)	1 (1.7)
S. haemoliticus	0 (0.0)	1 (2.1)	1 (1.7)
E. faecium	0 (0.0)	1 (2.1)	2 (3.4)
P. aeruginosa	2 (12.4)	1 (2.1)	1 (1.7)
E. coli	0 (0.0)	2 (2.3)	3 (5.2)
A. baumani	1 (6.3)	2 (2.3)	1 (1.7)
K. pneumoniae	0 (0.0)	1 (2.1)	0 (0.0)
Pr. mirabilis	0 (0.0)	0 (0.0)	1 (1.7)
A. lwoffi	0 (0.0)	1 (2.1)	0 (0.0)
Peptococcus	0 (0.0)	0 (0.0)	1 (1.7)
Peptostreptococcus	0 (0.0)	8 (17.0)	14 (24.1)
Clostridium	0 (0.0)	3 (6.4)	2 (3.4)
Bacteroides	0 (0.0)	6 (12.8)	3 (5.2)

**S. aureus* occurs significantly more often in the diseased cervical spine than in the thoracic ($p = 0.003$) and lumbar ($p = 0.001$) spine.

There is a tendency to increase in number of Peptostreptococci in the diseased lumbar spine ($p = 0.09$).

Table 6

Distribution of pathogens isolated from the lesion area by form of disease, n (%)

Pathogen	Form of disease		
	acute	subacute	chronic
*S. aureus (MSSA)**	23 (53.5)	7 (25.9)	13 (25.5)
S. aureus (MRSA)	1 (2.3)	0 (0.0)	3 (5.9)
S. epidermidis	4 (9.3)	2 (7.4)	8 (15.7)
S. saprophiticus	2 (4.7)	0 (0.0)	0 (0.0)
S. haemoliticus	1 (2.3)	0 (0.0)	1 (2.0)
E. faecium	0 (0.0)	1 (3.7)	2 (3.9)
P. aeruginosa	2 (4.7)	0 (0.0)	2 (3.9)
E. coli	1 (2.3)	1 (3.7)	3 (5.9)
A. baumani	3 (7.0)	0 (0.0)	1 (2.0)
K. pneumoniae	1 (2.3)	0 (0.0)	0 (0.0)
Pr. mirabilis	1 (2.3)	0 (0.0)	0 (0.0)
A. lwoffi	1 (2.3)	0 (0.0)	0 (0.0)
Peptococcus	0 (0.0)	1 (3.7)	0 (0.0)
*Peptostreptococcus**	0 (0.0)	10 (37.0)	12 (23.5)
Clostridium	0 (0.0)	2 (7.4)	3 (5.9)
Bacteroides	3 (7.0)	3 (11.1)	3 (5.9)

**S. aureus* is significantly more often isolated in acute form of disease than in subacute ($p = 0.009$) and chronic ($p = 0.012$) forms.

Peptostreptococci are isolated significantly more often in subacute ($p = 0.001$) and chronic ($p = 0.003$) forms of disease

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