IS TACTICAL ALGORITHMIZATION POSSIBLE FOR INFECTIOUS LESIONS OF THE SPINE? LITERATURE REVIEW

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Non-specific infectious lesions of the spine present a severe clinical problem due to the high risk of the septic complications and possible mortality. The late diagnosis and subjective treatment options could lead to complicated course of disease, progression of vertebral destruction, development of neurological disorders, as well as multi-resistance of bacteria due to the empiric antibacterial chemotherapy. The modern algorithms of diagnosis and treatment should be aimed at improving the quality of care for patients with infectious spondylitis. A literature review on the current concept of their assessment, including a step-by-step description of the Vertebral Osteomyelitis Guideline Team (VOGT) strategy, and the classifications of Pola (NCPS) and Homagk (SSC) is presented.

Key Words: non-specific spondylitis, spondylodiscitis, classification, emergency treatment.

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The strategies and measures related to treatment and diagnosis of patients with suspected spinal infection remain among the most disputable questions in modern spine surgery. That is probably why the national guidelines containing attempts to develop an algorithm for solving this problem either focus on its neurosurgical aspect only [1] or still are under interdisciplinary discussion [2], although in Russian clinical practice these patients are usually admitted to specialized departments (units to treat patients with purulent septic infections, injuries, and neurosurgical disorders).

Medical emergencies in infectious spinal pathology include

– the emergence and/or aggravation of neurological symptoms (myelopathy, caudopathy, or radiculopathy);

– sepsis; and

– severe pain (VAS score ⩾ 7) that can be eradicated by narcotic analgesics only.

Historically, the evolution of neurological disorders in patients with spondylitis has been attributed to mechanical compression of the spinal cord by spinal epidural abscess (SEA) which experimental model has been created by Feldenzer et al. [3] by direct injection of a bacterial agent into the epidural space, and/or with local microcirculatory disorders presenting as arteritis, arterial or venous thrombosis, septic thrombophlebitis of the spinal cord or their combination accompanied by hematic spread of infection [4]. Meanwhile, the vascular component in the pathogenesis of neurological disorders can prevail over the compression one [5]. For this very reason, the algorithms developed to diagnose and treat acute spinal infection must rely on the possibility that both components of myelopathy are present. There have recently been numerous attempts to elaborate such an algorithm.

The approach to surgical management in patients with spondylogenous sepsis, when the systemic inflammatory response syndrome is associated with paravertebral abscess rather than the epidural one or with the presence of extravertebral foci of infection, still remains not fully clear. The term «clinically significant (italicized by us) vertebrogenic abscess" that can be found in the literature means a structure requiring emergency sanitation because of the risk of decompensation of patient's overall condition regardless of other clinical symptoms [6] and largely represents a subjective evaluation.

In order to determine whether it is possible to develop an algorithm for therapeutic and diagnostic steps that need to be taken if spinal infection is suspected, we analyzed the publications retrieved using the PubMed, PMC, Google Scholar, and E-library search engines. A total of 179 publications available on the query date (April 15, 2020) were initially selected in accordance with the key words «spinal infection», «spondylodiscitis», «vertebral osteomyelitis», «purulent spondylitis», «classification», and their analogs in Russian. Having excluded the case reports and revised abstracts for full-text analysis, we ended up with 18 publications fully complying with the objectives of our analysis; focus was placed on studies published over the past decade.

We believe that the resulting data can be interesting for a wide circle of spinal specialists.

According to the recommendations of the Vertebral Osteomyelitis Guide-

line Team [7], diagnosis of spondylitis (regardless of whether it is accompanied by epidural abscess or not) should be based on proceeding from an assumption that the pathology is most unfavorable to the simpler variant. Therefore, the principle of incremental exclusion of the most threatening complications of the infectious process includes three critical components (the order in which they are listed corresponds to their importance):

(1) full neurological examination to confirm/exclude the corresponding disorders;

(2) evaluation of laboratory signs characterizing the infectious inflammatory process (complete blood count test, measuring the C-reactive protein level and erythrocyte sedimentation rate, blood chemistry test, blood and urine culture tests); and

(3) radiological examination (the degree of urgency at the inpatient medical facility depends on whether a patient has neurological disorders or not) (Fig.).

With allowance for this information, the authors have singled out four groups of clinical symptoms (Table 1) and ten risk factors (Table 2), which increase the probability of detecting spinal infection. They believe that most of these patients have at least one of the listed risk factors.

The following aspects are worth mentioning for the incremental algorithm of radiological examination of patients with suspected infectious spondylitis/epiduritis:

(1) the algorithm unfolds as a kind of descending ladder: from using the most sensitive method to reveal inflammatory changes and imaging the spinal cord structure (contrast-enhanced MRI) to analyzing the osseous structures of the spine (Table 3);

(2) if a patient has neurological impairment, it would be ideal to perform radiographic diagnosis within the first 2 hrs post admission; if no neurological impairments were detected, radiographic diagnosis should be performed within the first 6 hrs post admission;

(3) if radiographic data show an epidural abscess, it is necessary to start empirical antimicrobial therapy (Table 4) and consult a neurosurgeon as soon as possible;

(4) if radiographic data show signs of spondylitis and if hemodynamic instability is detected, the patient should start receiving antimicrobial therapy (Table 4); a decision should also be made whether the patient needs to consult a neurosurgeon; neurological examination should be performed every 4 hrs.

Conspicuous is the fact that blood culture test is the first stage in verifying a causative agent of infectious spondylitis; a biopsy of the pathology area should be performed within 24 hrs post admission. Meanwhile, the time of initiation of antimicrobial therapy depends on stability of patient's condition: the therapy is started without waiting for the results of blood culture test if the hemodynamics are unstable or after the hemoculture and its sensitivity were verified if the hemodynamics are stable.

Table 4 shows the regimen of the initial antimicrobial therapy recommended in this protocol.

According to VOGT recommendations clearly describing the algorithm of treatment and diagnostic measures to manage a patient with suspected spine/spinal canal infection, the question related to selecting an appropriate approach for surgical treatment is reduced to consultation of neurosurgeon.

It should specified separately that in hemodynamically unstable patients with sepsis, septic shock or severe and progressive neurological impairment, it is recommended to start empirical antimicrobial therapy and simultaneously attempt to make a microbiological diagnosis [8]. It is emphasized that although the regimens of antimicrobial therapy of spondylitis can vary, empirical therapy should be prescribed with allowance for circulating microbiota being predominant in a specific region (*S. aureus*, enterococcus, *Pseudomonas aeruginosa*, etc.) [8, 9].

Secondary epiduritis is a typical complication of spondylitis that may cause compression of the spinal cord and neurovascular structures and require using an active surgical approach as neurological deficit develops. The rate of secondary epiduritis ranges from 0.2 to 2.8 per 10,000 population [10–14]; diagnosis is usually complicated because of the nonspecific complaints of back pain. If acute neurological impairment was revealed, imaging of the infectious process must be immediately performed. In patients with nonspecific spondylitis, its detection meant a worse prognosis and lower patient's rehabilitation potential.

The data reported in systematic reviews focused on treatment of epidural abscesses, which were published in the issue of *Global Spine Journal* entirely devoted to spinal infections (2018, suppl. 4), demonstrate that early surgical treatment in combination with adjuvant antimicrobial therapy is the optimal approach only in patients with neurological deficit regardless of level of abscess localization [15, 16]. Isolated antimicrobial therapy is recommended for neurologically intact patients; however, treatment should be performed in a multidisciplinary inpatient clinic, and the patient needs to be notified that treatment of this pathology may require changing the treatment approach [17].

When surgical treatment of epidural abscesses is performed, spine stabilization is not an independent intervention and is conducted only if spinal instability is severe.

In our opinion, the most convenient tactical treatment algorithms for treating infectious spondylitis have recently been proposed by Pola et al. [18] and Homagk et al. [19] A.Yu. Bazarov [20] performed a comparative analysis of these algorithms in Russian, so we will not reproduce them word by word but rather dwell on the aspects that we find to be most important.

According to the classification of acute pyogenic spondylodiscitis proposed by Pola et al. (New Classification Pyogenic Spondylodiscitis, NCPS), the

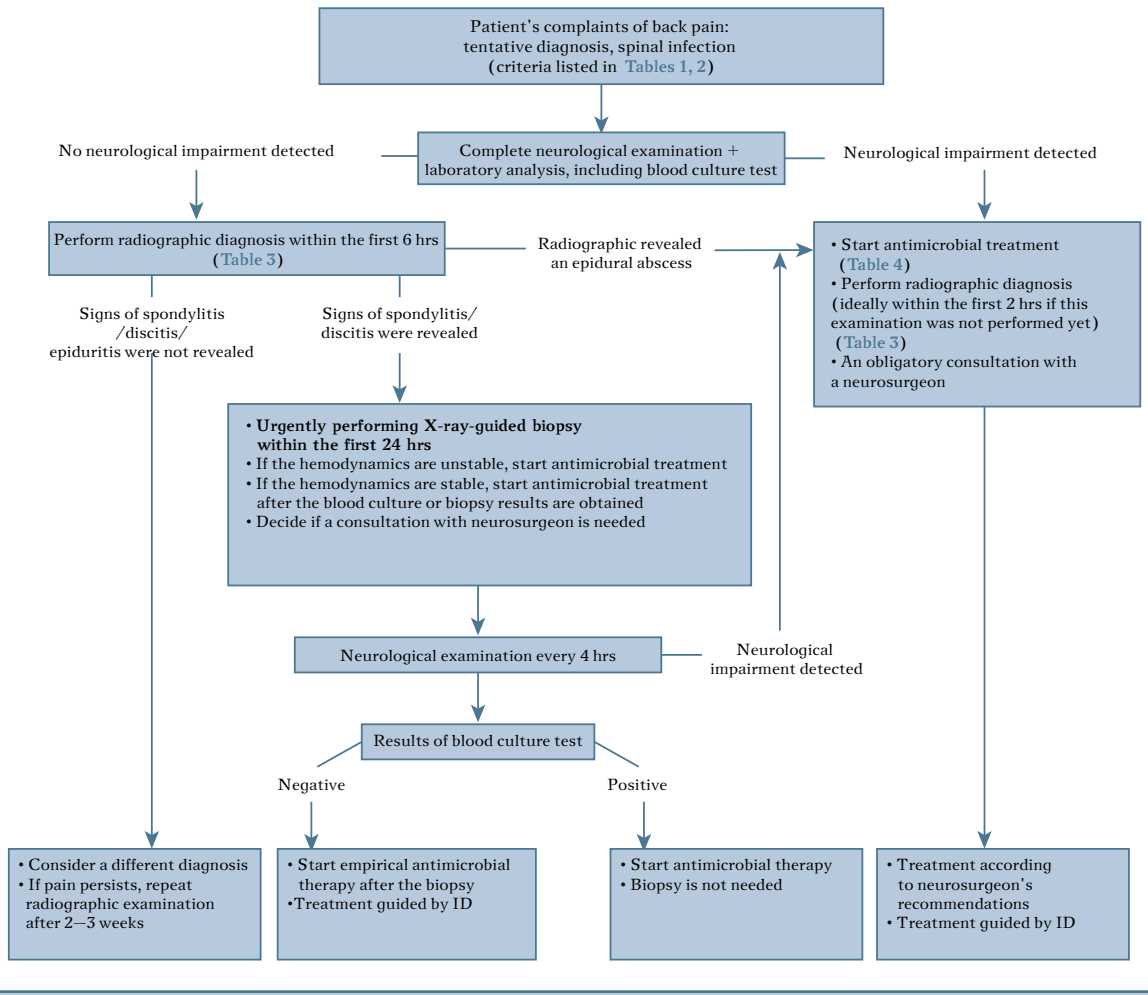

Fig.
Diagram of the tactical algorithm for diagnosis and treatment of infectious spondylitis/epiduritis (VOGT: ID – Infectious Diseases Service)

Table 1
Clinical symptoms increasing the probability that a patient has spondylitis or epidural abscess [7]

Clinical symptoms	Features
Back pain	Progresses gradually; tends to be exacerbated at night; has a definite localization; is associated with other systemic symptoms (anorexia, apathy/lethargy, weight loss, and nausea, vomiting)
Fever (temperature elevated above 38°C)	Is observed in 35–60 % of patients with spondylitis. NB! No fever does not mean that the patient does not have spondylitis
Focal neurological symptoms	Limb weakness; dysesthesias; radicular pain; gait disturbance; Bowel or bladder dysfunction
Symptoms vary with location of vertebral osteomyelitis / spinal epidural abscess	Dysphagia (for the cervical spine); autonomic disorders (for the thoracic spine)

Table 2

Risk Factors Increasing Suspicion for vertebral osteomyelitis / spinal epidural abscess [7]

Diabetes (the most common risk factor)
Any risk factors of bacteriemia, including administration of injectable drugs
Immunosuppression
Malignancy
Liver cirrhosis, chronic kidney disease, alcohol abuse
HIV/AIDS
Rheumatoid arthritis
History of back injury or a vertebral fracture
Recent spinal procedure
Infectious focus of any other localization

Table 3

Steps of the algorithm of radiographic examination if spinal infection is suspected [7]

Iterative steps of radiographic examination	Refinements and limitations for using the method
Whole-spine MRI with intravenous contrast	It is possible not to inject the contrast agent if it would excessively lengthen the examination
Whole-spine MRI	The examination is not performed if it is not feasible (e.g., because of patient's body constitution, the presence of an implant, etc.)
CT myelography	–
Whole-spine CT with intravenous contrast enhancement	–
CT of the spine	–

Table 4

Initial empirical antimicrobial therapy in patients with spondylitis/epidural abscess [7]

Preferred regimen	Vancomycin i.v.* + ceftriaxone 2 g i.v. every 12 hrs
Alternative regimen:	
if a pseudomonas infection is suspected or confirmed	Vancomycin i.v.* + cefepime 2 g i.v. every 8 hrs
if a patient has a penicillin allergy (non-anaphylactic-type)	Vancomycin i.v.* + meropenem (2 g i.v. every 8 hrs)**
if a patient has a severe penicillin allergy	Vancomycin i.v.* + aztreonam (2 g i.v. every 8 hrs)
if a patient is allergic or intolerant to vancomycin	Linezolid 600 mg i.v. every 12 hrs** + other antibiotic listed above

*personalized dose selection should be performed in patients with kidney failure;
**if approved by a clinical pharmacologist.
NB! On the one hand, these regimens are similar to those used to treat acute extravertebral pyogenic processes, while on the other hand, they are hardly available for extensive use in actual conditions in Russia because the drugs are not freely available and expensive

treatment approach is based on three main classification criteria: the visualizable vertebral destruction and related mechanical instability, neurological impairment, and paravertebral abscesses. The term «biomechanical instability» was defined as changes in segmental kyphosis angle at the affected level by more than 25 %. Taking into account the combination of the listed signs, the authors singled out three main types of lesions (A, B, and C).

Type A involves all the cases not accompanied by biomechanical instability, neurological impairment, or epidural abscess. Further division into subtypes depends on secondary criteria: A.1 – discitis without the involvement of vertebral bodies; A.2 – spondylodiscitis with the disc and bodies of the adjacent vertebrae being involved; A.3 – spondylodiscitis with limited involvement of paravertebral soft tissues; and A.4 – spondylodiscitis with unilateral or bilateral intramuscular abscesses.

It should be mentioned that when describing the main principles for treating patients with type A lesions (antimicrobial therapy and full-time wearing a rigid brace until the infection is completely eradicated), the authors suggest such surgical methods as minimally invasive transpedicular screw fixation (percutaneous transpedicular screw fixation) only (!) for patients placing high demands on quality of life.

Type B corresponds to patients with radiographically verified significant bone destruction or biomechanical instability without acute neurological deficit or epidural abscess. Therefore, the following subtypes of spondylodiscitis are differentiated: without segmental instability (B.1); without segmental instability but affecting the paravertebral soft tissues (B.2); as well as those with biomechanical instability and segmental kyphosis of different severity (B.3.1 < 25°, B.3.2 > 25°).

Pola et al. believe that in all the cases conservative treatment can be supplemented with percutaneous transpedicular screw fixation if the spine remains stable (B.1, B.2) and needs

to be accompanied by instrumented fixation in the cases of spinal instability. Meanwhile, the minimally invasive transpedicular screw fixation is proposed as an option for treating patients with mild kyphosis (B.3.1).

Type C embraces patients with epidural abscess, including those either having no neurological symptoms, without (C.1) or with (C.2) segmental instability, or having acute neurological symptoms without (C.3) or with (C.4) segmental instability. Patients without acute neurological symptoms and segmental instability (C.1) receive conservative treatment; thorough dynamic assessment of their neurological status is performed. The development of instability in these patients is regarded as a potential risk of neurological deficit (C.2), making it necessary to perform sanitation and surgical stabilization of the spine. Meanwhile, surgical decompression of neural structures in combination with segmental stabilization is always recommended for the patients with acute neurological symptoms (C.3 and C.4).

This classification can easily be reproduced, but in our opinion some provisions still need to be additionally refined:

– thus, the authors attribute the patients with radiographically verified significant bone destruction to type B. Unfortunately, they do not specify the criteria for evaluating the significance of bone destruction, which may make the evaluation subjective;

– confusion can be added by the fact that the division of type B.3 into subtypes differentiated according to biomechanical instability was related to segmental kyphosis angle (B.3.1 < 25°, B.3.2 > 25°), while the same segmental kyphosis (but presented in %) is a parameter showing whether biomechanical instability exists.

These discrepancies could potentially be reduced by using one of the three criteria of biomechanical instability in patients with hematogenous vertebral osteomyelitis, which were proposed by Herren et al. [21] almost simultaneously with publication of the Pola's classification:

– segmental kyphosis > 15°;

– vertebral body destruction by more than 50 % of its height;

– translational motion of a vertebra by ⩾ 5 mm.

The Homagk's tactical algorithm uses a numeric parameter characterizing the severity of spondylodiscitis (spondylodiscitis severity code, SSC) and takes into account almost the same key aspects related to their classification:

(1) whether instability of a functional spinal unit was formed as a result of bone destruction;

(2) whether a patient has neurological deficit; and

(3) whether the spine-adjacent structures are affected.

According to the answers to these questions, the authors identify three grades of spinal infection severity (Table 5).

Grade I vertebral osteomyelitis involves all the cases of infectious destruction diagnosed only according to clinical manifestations and MRI findings. The presence or absence of reaction of the paravertebral tissues is denoted with a letter A/B (Table 5); segmental kyphosis and spinal stenosis can also be present. Conservative treatment is recommended (3-month antimicrobial therapy). Internal fixation (except for instrumentation) of the affected vertebrae can also be used. Radiographic examination is performed 2 and 6 weeks after treatment initiation.

Grade II includes all the cases of spondylodiscitis with vertebral body destruction causing instability without neurological deficit. Surgical treatment involves internal fixation (for the thoracic and lumbar spine) in an attempt to correct kyphosis. After the surgery, 3-month antimicrobial therapy is prescribed with allowance for antibiotic sensitivity of the isolated bacteria. Follow-up CT scanning is performed 3 months later to evaluate the bone block formation (if the focus of infection was resected and spinal fusion was performed).

Grade III involves all the cases of spondylitis complicated by neurological deficit. The degree of bone destruction is less important. Surgical treatment is performed immediately after the diagnosis is made and consists of decompression of the spinal canal contents via laminotomy or laminectomy and fixation of the thoracic and lumbar spine. The focus of inflammation is resected through the costotransverse and posterolateral approaches; some patients are subjected to anterior stabilization (including using slow-release antimicrobial implants). Antimicrobial therapy lasts 3 months with allowance for the isolated bacteria; follow-up radiographic examination is performed 2 and 6 weeks after surgery.

The same researchers [22] recommend using the SponDT (Spondylodiscitis Diagnosis and Treatment) system to evaluate the severity of spinal inflammation. This system is based on grading three parameters: the level of C-reactive protein a biochemical inflammation marker (mg/dL); the VAS score for pain; and MRI findings. Each parameter is stratified according to its severity (Table 6); the treatment strategies depend on the overall results of stratification.

The total score < 3 is regarded as mild; score 3–5, as moderate; and score ⩾ 6, as severe form of spondylodiscitis. In accordance with this score, a decision is made which treatment strategies to choose (Table 7).

The authors present clinical data for 296 patients, in whom the treatment strategies depended on the grade of the disease (Table 7).

One of the features of the SSC classification is that it recommends performing anterior reconstruction in all patients with grade III spondylodiscitis. In this aspect, the approaches proposed by Pola and Homagk differ. Since the anterior stage is often more technically challenging for neurosurgeons (who usually have to deal with treating these patients), while the long-

term outcomes of isolated posterior instrumented fixation can be comparable to those of surgical treatment, A.Yu. Bazarov [20] recommends considering a trade-off variant (extending the dynamic follow-up of patients and monitoring the markers of inflammation). In his opinion, in some patients who had undergone posterior instrumentation simultaneously with antimicrobial therapy, spontaneous bone block is formed within 6–18 months (much earlier, Hadjipavlou et al. [23] demonstrated that it can happen within the period < 24 months). Clinical remission often makes it possible to postpone the consideration of the question regarding stepwise surgical treatment (anterior reconstruction) until later or even avoid using it in some cases [20].

Hence, it can be said that vertebrologists are currently attempting to develop an algorithm for decision making regarding diagnosis and treatment for patients with acute infectious spondylitis. The point to note is that different authors use the simplest and most reproducible clinical and radiographic criteria for this purpose; furthermore, the interpretation of these criteria can be made unbiased by using grading scales. This very approach might be logical in emergency situations, when diagnosis of the pathological process and correction of its most clinically significant complications is the main objective.

P.S. The authors considered it possible not to discuss the details of the regimens of antimicrobial therapy to treat infectious spondylitis, which have been discussed rather thoroughly in publications being analyzed here [2, 7–9, 19]. We would only like to emphasize that before prescribing the empirical treatment, the physician needs to actively search for the pathogenic bacteria, start therapy with intravenous infusion of the drugs, and take into account the microorganisms typically occurring in the specific region. Speaking about the duration of antimicrobial therapy, the period of 6–8 weeks is usually recommended to treat active nonspecific spondylitis [2, 7–9], although some authors believe that treatment should be much longer [19]. However, we suppose that it is an independent question lying beyond the scope of this review.

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Table 5
SSC classification of vertebral osteomyelitis [19]

Disease severity grade	Clinical radiological criterion		
	bone destruction and instability	acute neurological deficit	involvement of paravertebral tissues
I	No	No	A/B
II	Yes	No	A/B
III	Yes/No	Yes	B

Table 6
Stratification of the criteria of inflammation in patients with spondylodiscitis according to their severity (the SponDT system) [22]

Criterion	Score for symptom severity			
	0	1	2	3
CRP, mg/dL	<10	<50	51–150	>150
Pain (VAS score)	<3	3< ... <5	5< .... <8	≥8
MRI signs of spondylodiscitis	None	Without destruction	With destruction	With abscess

Table 7
Spondylodiscitis severity classification (SSC) according to clinical and radiological findings and selecting the treatment strategy [19]

Severity	SponDT score	Neurological deficit	Bone destruction	Treatment modality	
				surgical treatment	antimicrobial therapy
I	<3	No	No	Not indicated or posterior stabilization, biopsy	12 weeks
II	3–6	No	Yes	Posterior stabilization, biopsy, repositioning, sanitation of the paravertebral tissues, ventral stabilization as the second stage	12 weeks
III	>6	Yes	Yes	Posterior stabilization involving laminectomy, discectomy through the posterior approach + histological examination, topical antimicrobial treatment, sanitation of the affected paravertebral tissues, early ventral stabilization	12 weeks

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