

Spondylodiscitis: is really all well defined?

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Abstract. – The term spondylodiscitis describes the infection of both the intervertebral disc space and the adjacent vertebrae. Pyogenic Vertebral Osteomyelitis (PVO) is more common in older patients (mean age 59-69 years) with a male preponderance (52-69%). Recent studies reported an alarming increase of incidence over the last 20 years, due to the increase of diagnostic sensibility, the increase of the average lifetime and to the consequent association of chronic disabling pathologies, of immunosuppression, of surgical or invasive procedure. Improvements in radiological diagnosis, surgical techniques, and management of antimicrobial therapy have greatly improved PVO clinical outcome, but morbidity remains significant mostly because of the delay of diagnosis. The non-specific features of this infection can lead to underestimate the patient conditions, ending to a significant delay in diagnosis, reported from 30 to 90 days, and consequently to severe impairments, such as spine deformity and permanent neurological deficit. The duration of medical treatment is not yet established, and further randomized trials are needed to define it.

Key Words:

Pyogenic vertebral osteomyelitis, Diagnosis, Surgical techniques and management.

Introduction

Spondylodiscitis is an infection of both the intervertebral disc space and the adjacent vertebrae. Pyogenic vertebral osteomyelitis (PVO) is more common in older patients (mean age 59-69 years) with a male preponderance (52-69%)¹.

Recent studies reported an alarming increase of incidence over the last 20 years², due to the more sensitive diagnostic techniques, the increase of the average lifetime. This leads to the consequent

association of chronic disabling pathologies, of immunosuppression, of surgical or invasive procedure.

Improvement in radiological diagnosis, surgical techniques, and management of antimicrobial therapy have greatly improved PVO clinical outcome, but diagnostic delay still affects the morbidity.

The non-specific features of the infection can lead to underestimate the patient conditions, ending to a significant delay in diagnosis, ranging from 30 to 90 days³, and consequently to severe impairments, such as spine deformity and permanent neurological compromise.

Clinical features

Since its non-specific clinical manifestations, vertebral osteomyelitis still represents a clinical challenge. The onset is insidious, with back pain as the most common symptom (67-100%)⁴. The spinal pain is typically localized on the infected area and gradually increases in intensity, becoming non-responsive to analgesics. Physical examination can reveal mild tenderness over the spinous process of the involved area, a decreased range of motion and sometimes spasms in the paravertebral muscles. Fever is less common and occurs in about 30-50% of patients^{1,5}.

In one study of 70 patients, weakness appeared to be the second most frequent symptom⁶.

Neurological impairment is reported in 33% up to 79% of cases, and it can be caused by vertebrae collapse, spread of the infection underneath the posterior longitudinal ligament or by frank epidural abscess with compression of the spinal cord⁷.

Generally, spondylodiscitis results from haematogenous seeding of an infection and the initial symptoms and signs could be frequently dominated by the primary infection site, such as urinary tract or skin and soft tissue.

Imaging

Imaging plays a crucial role in defining the correct diagnosis.

Traditional radiography (RX) lacks in specificity (57%) and accuracy (73%)⁸. CT-scan shows a sensibility of 67% and a specificity of 50%, and it detected abnormalities in 94% of patients in a previous review^{3,9}, but it allows a limited evaluation of soft tissues¹⁰.

Currently, MRI represents the gold standard imaging modality for diagnosing vertebral osteomyelitis, and it is recommended for its high sensibility, specificity, and accuracy (96%, 92%, and 94%)⁵.

MRI also provides insight into the spinal cord and epidural space, allowing the evaluation of the extension of the infectious process through the soft tissues and the presence of epidural abscess¹¹. MR with gadolinium contrast may be the best option to highlight the extent of soft tissue and bone phlegmon and abscess.

¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) PET scan is one of the alternative diagnostic imaging modalities recommended, especially in cases when MRI cannot be conducted, and it is particularly useful for differentiating lumbar spine infection from degenerative changes because of its excellent sensitivity¹².

Imaging During Follow-up

Imaging control to determinate the treatment response is still unclear, since radiographic evidence of ongoing inflammation may persist for months to years in patients without any clinical implication. The radiological investigation should never be conducted before 4 weeks after treatment, because of the high rate of false positive, even if clinical improvements are not present^{4,13}.

An important and early sign of therapeutic success is a decreased signal following the administration of contrast, mostly in soft tissues.

A radiological follow up with MRI could be useful in patients with higher risk of developing disabling sequelae (e.g., spine instability, deformities), occurring even after the resolution of the infectious process.

Difference in Etiology

Many authors questioned if etiological agents could be linked to differences in clinical or radiological sense.

Gram-negative bacilli have been isolated with a higher incidence in older patients of female sex, especially with a history of a recent or recurrent

UTI, or cancer (chemotherapy/radiotherapy induced alimentary mucositis)^{14,15}.

Moreover, Gram-negative bacteria tend to manifest with constitutional symptoms (fever and drowsiness), with or without back pain, while on the other hand, Gram-positive bacteria cause more frequency to back pain and epidural abscess.

In terms of laboratory markers of inflammation, patients with MSSA (methicillin-sensitive *Staphylococcus aureus*) hematogenous vertebral osteomyelitis (VO) are more likely to have higher C-reactive protein (CRP) values¹⁵.

No difference in outcome is generally reported between Gram positive and Gram negative PVO, except for *Staphylococcus aureus*, reported by many authors as an independent risk factor for treatment failure^{16,17}.

Blood Tests

Erythrocyte Sedimentation Rate (ESR) and CRP are widely used in the initial diagnosis and in the further management of VO. The majority of papers report alterations of both, ESR and CRP, while white blood cell counts (WBC) showed less sensitivity, being elevated in only 42.6% PVO cases^{1,18}, thus resulting as an unreliable laboratory marker in the diagnosis of many spinal infectious processes¹¹.

Fever and persistently high CRP values were significant risk factors associated with treatment failure¹⁹.

An important evaluation of the treatment is often carried on at the fourth week after initiation of antibiotics therapy and the values of CRP and ESR can provide meaningful information. CRP reduction of at least 50%, along with clinical improvements, has proven to be good prognostic parameters and markers of effective antibiotic therapy^{11,20}.

However, we underline that CRP is not a specific marker of infection and it could be modified by other inflammatory condition; therefore, it should be interpreted, considering the whole patient's clinical evolution.

Little is known about vertebral osteomyelitis with a negative CRP at baseline. It is unclear if there are differences in terms of etiology, diagnostic delay or outcome when compared to those with a CRP alteration. In these cases, follow up is generally based on clinical and radiological changing.

Microbiological Diagnosis

Microbiological diagnosis is the cornerstone for the optimal management of PVO, enabling an antimicrobial treatment targeted on the causative

pathogen. Etiologic diagnosis can be achieved in several ways.

Blood cultures

Bacterial and fungal blood cultures have good sensitivity in PVO, ranging between 36-72%, even higher than CT-guided biopsy²¹, but lower than surgical biopsy^{22,23}.

Higher sensitivity is obtained collecting blood samples before starting an empirical antimicrobial treatment, even if the patient is afebrile. Some authors routinely perform blood cultures ever after every invasive procedure, but up to now, there's no evidence supporting this suggestion¹⁹.

CT-guided Biopsy

When to perform a CT-guided biopsy?

The Infectious diseases society of America (IDSA) recommends an image-guided aspiration biopsy in patients with suspected vertebral infection (based on clinical, laboratory, and imaging studies) when a microbiologic diagnosis for a known associated organism has not been established by blood cultures or serologic tests⁴.

Aspiration biopsy may lead to a microbiologic diagnosis and obviate the need for open surgical intervention in 50%-60% of cases or more²⁴⁻²⁷.

According to IDSA guidelines, a positive blood culture for organism typically associated with native vertebral osteomyelitis (NVO) (such as *Staphylococcus aureus*, *Staphylococcus lugdunensis*, and *Brucella* species) it is possible to obviate the need for an image-guided biopsy⁴.

A sustained bloodstream infection with other coagulase-negative staphylococci in a patient with suspected PVO receiving chronic hemodialysis or in patients with infected intravascular devices may also obviate the need for image-guided aspiration biopsy^{28,29}.

A suspected PVO with a concomitant bloodstream infection with another organism (e.g., *Candida* species, *Enterobacteriaceae*, streptococci, *Pseudomonas* species) should be interpreted in relation to patient's history, symptoms, imaging findings. In these cases, there are no universal guidelines, and therefore the choice of performing a CT-guided biopsy for diagnostic confirmation is left to the discretion of the treating physician⁴.

When to Perform a Second CT-Guided Biopsy?

Many studies³⁰⁻³² suggest that a second biopsy may be useful if no pathogen is identified after the first attempt.

Blood culture's sensibility after a first negative biopsy seems modest, while a second percutaneous needle biopsy could identify PVO etiologic agent in 30 up to 80% of cases³¹.

Whenever a causative organism couldn't be found after multiple image-guided biopsies, physician should take in consideration surgical sampling, which seems to have the highest culture positive rate, even when minimally invasive techniques were used⁸, and it could represent a valid option especially in patients with paravertebral abscesses.

Which Tissue is Better?

In a retrospective cohort study of 128 patients affected by PVO with soft-tissue abscesses, the culture positive rates of vertebral bodies and soft tissues were 39.7% and 63.5%, respectively, showing the second ones as the best site for a needle biopsy. Among soft tissues, the culture positive rates of intervertebral discs, paraspinal abscesses, and psoas abscesses were 52.9%, 70.6%, and 58.3%, respectively³³.

How Long Should Antimicrobial Therapy be Stopped before CT-guided biopsy?

The culture of bioptic material's sensibility is reduced by previous antibiotic exposure^{4,26,34-35}.

For this reason, many authors recommend deferring empiric antimicrobial treatment of NVO, with the exception for life-threatening conditions or risk of permanent neurological damage, until a diagnostic image-guided aspiration and/ or biopsy of the affected area is obtained⁴.

The optimal duration of the suspension of antimicrobials should depend on the half-life of the antibiotic used and its postantibiotic effect. Holding antibiotics when feasible for 1-2 weeks seems reasonable^{4,36}.

Molecular Test

Molecular tests performed on tissue specimen are especially useful for the microbiological diagnosis. Polymerase chain reaction (PCR) was found in one study to have high sensitivity, specificity, and accuracy (95%, 83%, and 92%, respectively) in detecting *M. tuberculosis*³⁷⁻³⁹.

Ho Choi et al showed that, compared to conventional culture in the etiological diagnosis of vertebral osteomyelitis 16S rDNA PCR was approximately 2 times more sensitive³⁹. A fastidious organism such as *Clostridium perfringens*, *Streptococcus dysgalactiae*, and *Haemophilus parainfluenzae*, was detected only by PCR.

In addition, in the same study positive rate of culture seemed to be more affected by prior exposure to antimicrobial treatment compared to those of PCR; thus, PCR seems more sensitive tests for the patients with antimicrobial exposure.

Physicians must keep in mind, however, that PCR could lead to false positive results due to contamination during specimen collection or to the PCR process itself.

Since the high costs and the relative availability, guidelines for performing 16S rDNA PCR on vertebral bioptic tissue are not yet been universally defined. It seems reasonable to retain this diagnostic technique for culture-negative spondylodiscitis and for biopsy performed under antimicrobial treatment.

Culture-Negative Pyogenic Vertebral Osteomyelitis

According to the main published retrospective cohorts of PVO^{19,22}, the etiologic diagnosis is achieved only in 49.7-74.3% of spondylodiscitis despite invasive diagnostic procedures. Possible explanations may be: underlying presence of fastidious bacteria, antibiotic exposure prior to obtaining an adequate specimen, false-negative biopsy of the infected site (sampling error, compartmentalization of infected foci into the bone) or low-grade infections (may be due to lower inoculums of pathogens).

Despite the proportional relevance of culture-negative PVO, only a few publications focused on diagnosis and treatment in these cases.

A universally accepted definition of culture-negative PVO is still lacking: some authors considered only the presence of a compatible clinical and radiological illness. This may lead to misinterpretation of non-infectious pathologies as PVO.

A further useful diagnostic tool may be the histopathologic examination of a spinal tissue sample, able to distinguish between pyogenic and granulomatous disease. Additionally, it may reveal a potential underlying malignancy.

However, no histopathologic criteria are universally accepted to distinguish between infectious and non-infectious vertebral inflammatory processes such as: seronegative spondyloarthropathies (consisting principally of ankylosing spondylitis, psoriasis, Reiter's syndrome, and certain intestinal diseases), adult-onset rheumatoid arthritis, and juvenile chronic arthritis, Modic vertebral endplate and marrow changes and osteodegenerative processes.

Many authors reported that culture-negative PVO is more likely to be less symptomatic. They have also fewer coexisting medical conditions spinal procedures prior to diagnosis are more frequent and are associated with a longer diagnostic delay.

The mean CRP recorded at the time of presentation was also significantly lower in this group (96 vs. 157 with a $p=0.004$). These data may support previous studies speculating about lower inoculums of pathogens in culture-negative PVO^{19,44,45}.

The outcome of culture-negative PVO is still a matter of debate: in Table I and Table II we report a literature review.

It is therefore unclear whether outcomes are different in culture-negative PVO, and this may be due to two possible reasons. Either the patient is less severely affected or affected by a lower inoculum infection, in which case outcomes may be better, or they had the infection but the search for a causative organism was suboptimal (for example due to the prior use of antibiotics), and this may worsen outcomes.

The choice of antibiotics for culture-negative PVO should include broad-spectrum antibiotics with a favorable bone penetration, seeking activity against *Staphylococcus aureus* and gram-negative organisms according to the patient history²⁰. As previously established, the predominant pathogen in PVO was *Staphylococcus aureus*, with a wide geographical differences in rates of methicillin-resistance, also according to main recognized risk factors: infective endocarditis, presence of a central intravascular catheter, and hemodialysis¹⁹. This choice should also take into account the etiological setting (potential portal of entry and patient-related factors promoting the development of specific organisms) and the antibiotics used prior to the diagnosis, if any.

The optimal total duration of antibiotic treatment in this setting is a controversial topic as well. There's only one retrospective cohort, published by Kim et al²⁰, suggesting that prolonged antibiotic therapy for at least 8 weeks might be required in culture-negative PVO.

Special Issues

Brucellosis

Brucellosis serologic testing is warranted in presence of determined high-risk conditions, such as: residence in endemic countries (Mediterranean basin, Persian gulf, Indian subcontinent, some areas from central and South America), ingestion of unpasteurized milk or cheese, contact with ani-

Table I. Published data supporting worse outcome for culture negative PVO.

Author (year)	Country	Population number (culture-negative vs. known etiology)	Results
Hopkinson N et al (2001) ⁴⁶	UK	4 vs. 18 patients	Culture negative PVO had a poorer outcome: one death and three with increased morbidity.
Hopkinson N et al (2016) ⁴⁷	UK	6 vs. 17 patients	Culture negative PVO had an increased treatment length from an average of 77 days (15 % > 100 days) to 142 days (60 % > 100 days) ($p = 0.054$). Length of hospital stay was similar.
Pola et al (2018) ²²	Italy	52 vs. 155 patients	Culture negative PVO was a negative prognostic factor (OR 0.41; 95% CI 0.19-0.87; $p = 0.02$), confirmed by multivariate analysis (AOR 0.26; 95% CI 0.10-0.65; $p = 0.004$).

Table II. Published data supporting no outcome difference for culture-positive vs. negative PVO.

Author (year)	Country	Population number (culture-negative vs. known etiology)	Results
Gillard J et al (2005) ⁴⁵	France	8 vs. 18 patients	None of culture-negative PVO experienced relapses or recurrence, whereas relapses occurred in 3 controls
Lora-Tamayo J et al (2011) ⁴⁸	Spain	25 vs. 47 patients	No differences were found between both groups in the outcome (93% success, 22% sequelae).
Kim J et al (2014) ¹⁹	South Korea	76 vs. 75 patients	Rate of treatment failure tended to be lower in culture-negative PVO [9.2% (7/76) vs. 17.3% (13/75); $p = 0.157$]. The overall relapse rate was 6.6% and did not differ significantly between groups
Tachibana T et al (2014) ⁴⁹	Japan	25 vs. 15 patients	No significant difference in mortality (8.0% vs. 13.3%)
Kasalak Ö et al (2018) ³²	The Netherlands	39 vs. 25 patients	Outcome within 6 months (development of neurologic or orthopedic complications, surgery, and death) was not significantly different ($p = 0.751$).

mal tissues or presence of a subacute back pain, associated with unexplained fever, fatigue and arthralgias.

Brucella spp agglutination test is the most frequently used, and titrations up to 1/160 indicate a *Brucella* infection and increase during infection period. Other serological tests are Rose-Bengal

test, Coombs anti-brucella test ($> 1/320$), and ELISA test which is the most specific one.

In systemic brucellosis, the diagnostic gold standard is a bacterial culture of specimens taken from bone marrow, liver, CSF, joint fluid and blood. PCR is a further diagnostic technique with a very high sensitivity⁴⁰.

Tuberculosis (TB)

Non-invasive tubercular diagnostic tests, such as a purified protein derivative (PPD) test or obtaining an interferon- γ release assay (e.g., Quantiferon-test), should be performed in every patient born or being resident in a highly endemic region, reporting a previous TB contact, showing any risk factor for TB (HIV/AIDS, pathologic chest radiograph, diabetes, etc.) or reporting suspect signs or symptoms (low-grade fever, cough, weight loss, night sweats or hemoptysis).

Every patient with a PPD or IGRA positivity and a suspect spondylodiscitis should undergo a microscopic for acid-fast bacilli, with a PCR for *M. tuberculosis* and mycobacterial culture on vertebral biopsy samples or other infected tissue (bronchoalveolar lavage, lymph nodes, etc.)^{41,42}.

Coxiella Burnetii

Q fever is a worldwide zoonosis, caused by *Coxiella burnetii*, an uncommon organism that may be found in cattle, sheep, goats, and other domestic mammals. The infection results from inhalation of a spore-like small-cell variant, and from contact with milk, urine, stools, and other biological liquids of infected animals. The disease is rarely tick-borne.

Clinical symptoms might be non-specific, often with a mild aspecific flu-like syndrome, while the chronic infection is rare and typically includes endocarditis and osteomyelitis.

The main differential diagnosis is a mycobacterial infection, based on the histological granulomatous presentation of lesions. Whereas serology is the reference diagnostic method for Q fever, detection of *Coxiella burnetii* in tissue specimens by PCR and cell culture provides useful additional evidence of infection. Culture-negative osteoarticular samples with granulomatous presentation upon histological examination should raise suspicion of Q fever. Treatment is the same for endocarditis and osteitis (doxycycline and hydroxychloroquine for almost 18 months), but a lifelong prophylaxis might be planned in special cases^{42,43}.

Treatment length

Optimal treatment length for PVO is also a matter of controversies. In the past years, most experts agreed on a standard treatment duration for PVO of at least 12 weeks, given the limited antibiotic penetration into the bone and the need for several weeks for the bone to revascularize. However, more recently some small retrospective

cohorts suggested that a shorter antibiotic course may be equally effective, at least in some special population of patients^{50,51}.

In 2015, Bernard et al¹⁷ published a multicenter, open label, noninferiority randomized controlled trial demonstrating no difference in cure rates between 176 patient with microbiologically proven PVO treated with a 6-week targeted antibiotic treatment vs. 175 comparable patients treated for 12 weeks.

However, in this study non-inferiority of a 6-weeks treatment was not demonstrated in some subgroups where a longer treatment length may be considered: age >75 years, immunosuppression or diabetes, endocarditis and presence of neurological signs.

Some limitations of this study include the low incidence of spinal abscesses (only 19% of enrolled patients) and the low incidence of MRSA (only 5.5%).

Furthermore, no information is provided on optimal treatment length in surgical patients.

One year later, Park et al⁵² published a retrospective cohort of 314 patients with microbiologically proven PVO, demonstrating that patients with at least one risk factor for recurrence (MRSA PVO, undrained paravertebral abscess of end-stage renal disease) should be treated for ≥ 8 weeks. In the absence of these risk factors, the likelihood of relapse in patients treated for < 8 weeks was much lower.

In this scenario, no standard treatment can be proposed for PVO, but therapy should be individualized on patient's risk factors, on radiologic findings (e.g., abscess), on etiology and considering clinical and biochemical follow-up (normalization of sign, symptoms and inflammatory markers)⁵³.

Treatment administration route (endovenous vs. oral)

Given the poor antibiotic penetration into bone tissue, many experts suggest treating PVO with a parenteral course of antimicrobial therapy in order to achieve the best PK/PD.

However, prolonged intravenous (IV) treatment for bone infections implies management difficulties, major cost and especially adverse event related to parenteral infusion.

Oral antimicrobials with excellent bioavailability, including fluoroquinolones, rifampin, linezolid, tetracyclines, and metronidazole, allow the possibility of an early switch to the oral route without compromising efficacy.

Until now it remains unclear the best timing for shifting the antimicrobial therapy to an oral administration.

A retrospective cohort study⁵⁴ of 61 patients with PVO, a switch to an oral antimicrobial therapy was performed in 72% of patients after a median intravenous therapy of 2.7 weeks. In this small cohort⁵⁴, no recurrence was observed, provided drainage of epidural or paravertebral abscesses and improvement of inflammatory markers.

More recently many authors reported no outcome difference between i.v. and oral antimicrobial therapy for staphylococcal osteomyelitis⁵⁵⁻⁵⁸.

Further studies are necessary to ascertain the effective need of initial i.v. treatment and its duration.

In any case, considering the elevated complexity of PVO treatment, we always suggest a supervision by an infectious disease specialist.

Conclusions

The management of pyogenic vertebral osteomyelitis has greatly improved during the last decades, leading to better outcomes. However, several questions are yet to be answered to improve mortality and disability that still affect the patients.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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