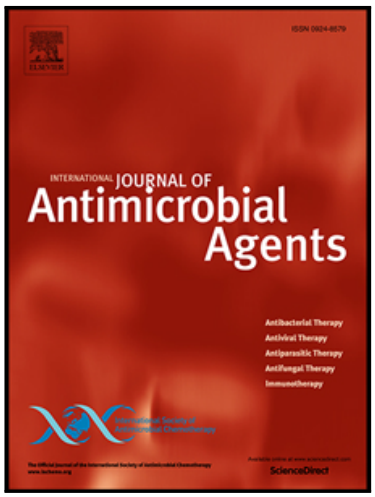

Hot Topics on Vertebral Osteomyelitis from the International Society of Antimicrobial Chemotherapy

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Hot Topics on Vertebral Osteomyelitis from the International Society of Antimicrobial Chemotherapy

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Summary:

Vertebral osteomyelitis (VO), also known as spondylodiscitis, describes infections of the vertebrae and intervertebral discs. Discitis describes infection limited to the intervertebral discs; in clinical practice both discitis and VO can be regarded as different stages of a single entity. VO can be caused by bacteria, fungi and parasites The incidence of VO is increasing globally representing 3-5% of all osteomyelitis with an estimated incidence ranging from 4 to 24 per million per year. Increasing incidence has been attributed to a combination of improved diagnostics, increased healthcare associated infections, haemodialysis, indwelling catheters, intravenous drug use, spinal instrumentation, immunocompromised hosts and an ageing population [1].

If left untreated, VO can lead to irreversible spinal cord injury, deformity, neurologic deficits, septicaemia, and mortality (mortality rates ranges 4%–29%). VO is typically treated with antibiotics, but up to 40% to 50% of VO patients may eventually require surgical intervention [1–3]

Despite advances in diagnostic modalities, medical and surgical care, there are still many controversial areas with regards to both diagnostic and therapeutic strategies in VO. In this review a number of 'hot topics' on VO were selected and reviewed by members of the Skin, Soft Tissue and Bone Infections Working Group of the International Society of Antimicrobial Chemotherapy (ISAC). This group includes international scientists, microbiology and infectious diseases clinicians and academics, whose aim is to advance the education and the science of infection management. This paper is an in-depth review of the current literature, providing a summary of the various aspects of VO and expert opinions and insights from the authors' own experience, highlighting areas for future study and research.

Key words:

Brucella, vertebral osteomyelitis, spondylodiscitis, Spinal Tuberculosis, fungal infections

1A Clinical findings of vertebral osteomyelitis

Vertebral osteomyelitis (VO) is clinically characterized by pain along the spinal area affected with or without fever. Focal back or neck pain is relatively common; occurring in most of cases, but up to 15% of patients may have no back pain. The pain can be acute or gradual in onset, progressing and worsening over several weeks to even months. Pain is typically exacerbated by physical activity, percussion of the affected area and more noticeable at night. The mean duration of symptoms is 48 +/- 40 days. Rarely a mass or spinal deformity may be clinically visible. Spinal deformities, such as kyphosis and gibbus deformity, are more frequent when the etiology is tubercular [1,4–6].

Radicular pain may radiate to the chest, abdomen, leg, scrotum, groin and perineum. Spine movements are often limited due to localized spinal pain and muscle spasm. Extension of infections posteriorly into the epidural space, leads to worsening back pain with radiculopathy and motor weakness and sensory changes and potential paralysis [7].

Physical examination can reveal signs of psoas abscess (e.g. flank pain and pain with hip extension) and neurologic signs in the lower limbs, and palpation for distended bladder. Abscess of cervical spine can be characterized by cervical rigidity, dysphagia or torticollis. Abscesses of the lumbar spine can spread through the ischiatic foramen and involve gluteus muscles. When lower lumbosacral roots are involved the “cauda syndrome” can appear. Sinus formation can be the result of a long-standing unrecognized infection [8].

Symptoms can be more non-specific in children: irritability, limping gait, hip pain, rejection to crawl, sit or walk, even abdominal pain and incontinence may also be present. Crucial signs include loss of lumbar lordosis and lower back movements; neurological deficits are unusual.

Fever is much less frequent than back pain: it occurs in only about half of patients. It is uncommon in mycobacterial, brucellar, or fungal VO and may be masked in patients on therapy with analgesics with antipyretic effects. However fever is common in older children with VO. Cervical infections,

tuberculosis VO and late diagnosis are often associated with systemic symptoms of weight loss, weakness and anorexia [1,4,5].

1B Imaging for vertebral osteomyelitis.

Plain radiographs are often normal in the early phases, abnormal findings are usually not apparent before three weeks or more after the onset of symptoms. Frequent lesions include lysis of two contiguous vertebral bodies with collapse of the intervening disc space [9].

CT findings of VO appear earlier than those seen on plain radiographs. Main abnormalities include end plate irregularities. CT is especially useful for detecting bony sequestra and soft tissue abscesses, and to exclude epidural abscesses [10]. CT scan can also be useful for guiding vertebral biopsies. CT remains the first-line alternative test when MRI is not available or feasible [1].

MRI is the most sensitive imaging test for confirming VO diagnosis [10]. Abnormalities are often detected earlier on MRI than on CT. Typical findings on MRI include i) decreased signal intensity in the vertebral bodies and disc and loss of endplate definition (T1-weighted images), ii) increased disc signal intensity and/or increased vertebral body signal intensity (T2-weighted images), iii) contrast enhancement of the vertebral body and disc. Multi-sequence sagittal MRI of the entire spine may be helpful in patients with known single-level spine infection [11]. Follow-up by imaging including MRI is not recommended routinely. It should be only proposed for patients whose clinical status has not improved at the planned time for discontinuation of antibiotics in order to evaluate for the presence of an abscess in need of drainage or to detect spinal instability amenable to surgical intervention [1].

Radionuclide scanning [12]

- **Three-phase bone scintigraphy** using labeled technetium is neither sensitive nor specific enough for the diagnosis of vertebral osteomyelitis. False negatives have been reported mainly in the elderly. Therefore, bone scanning should not be used routinely in this setting.

- **Gallium scan;** Osteomyelitis is likely if there is greater tracer uptake in the gallium scan compared to the three-phase scan. Conversely, if the gallium scan is normal, then osteomyelitis is unlikely, regardless of the bone scan findings. The main limitation of gallium scans are that they take 48–72 hours to complete, necessitating multiple visits to the nuclear medicine department.
- **Labeled-leukocyte scan** is not recommended for the diagnosis of vertebral osteomyelitis due to poor sensitivity and specificity values.
- **Positron emission tomography (PET) scanning using 18-fluorodeoxyglucose (FDG), combined with CT (PET-CT);** During recent years many studies investigating the potential role of fluoride oxyglucose-positron emission tomography/computed tomography (FDG-PET/TC) for the management of a wide spectrum of infectious diseases, including VO, have been published, with promising results [13]. Current Infectious Diseases Society of America (IDSA) guidelines recommend the use of FDG-PET/TC for the diagnosis of spondylodiscitis only when MRI cannot be obtained (e.g. patients with implantable cardiac devices, cochlear implants, claustrophobia, or in case of MRI unavailability) [1]. Although MRI still represents the gold standard technique for the diagnosis of spondylodiscitis, higher sensitivity and specificity values have been recently reported for FDG-PET/TC compared with MRI (95% and 88% for FDG-PET/TC and 85% and 66% for MRI, respectively) [14,15]. However, false positive have been attributed to tumor, degenerative spinal disease, and/or spinal implants. Moreover, FDG-PET/TC has been associated with a higher diagnostic value compared with MRI for the detection of early spondylodiscitis within two weeks after symptoms onset [16]. Another important advantage of FDG-PET/TC over MRI is represented by the identification of metastatic foci of infection, especially in patients with bacteremia, allowing a prompt source control [14]. Conversely, MRI is more sensitive than FDG-PET/TC for the evaluation of soft tissue involvement and for the identification of small epidural abscesses [14]. To note, FDG-PET/TC is useful not only for the diagnosis of pyogenic spondylodiscitis, but also when mycobacteria, fungi or *Brucella* are

involved, with some data showing different uptake values according with the etiology of infection [13]. Specifically, higher uptake values have been reported in tuberculous spondylodiscitis compared with pyogenic one [17].

The evaluation of response to antibiotic treatment in patients with spondylodiscitis represents an investigational role for FDG-PET/TC [13]. Overall, a significant improvement of FDG-PET/TC uptake values after 6 weeks of an adequate antibiotic treatment has been reported in patients with spondylodiscitis, but few data specifically addressing this topic are available so far [18,19]. A residual persistence of FDG uptake has been frequently reported also after an adequate course of antibiotic treatment, and the most appropriate interpretation of these data is matter of debate. Particularly, the pattern of residual activity seems to be crucial to distinguish between a mechanically induced residual inflammation, characterized by FDG uptake confined to the margins of the disc, and active infection, with FDG uptake extended to bone and soft tissues[19].

1C Microbiologic investigations for vertebral osteomyelitis

The corner stone for microbiologic diagnosis is specimen culture obtained from a biopsy. A microbiologic diagnosis should be obtained to target antimicrobial treatment. But in special circumstances including neurologic compromise and sepsis, prompt empiric antibiotic therapy is warranted. However in patients with clinical, biochemical and imaging studies suggesting VO with positive blood cultures for *S. aureus* or *S. lugdunensis*, then biopsies are not shown to add additional diagnostic value [1].

Blood cultures (at least 2 sets, aerobic and anaerobic bottles) are recommended. The correlation of blood cultures with cultures results from biopsy has been shown to be high for *S. aureus* and *S. lugdunensis*, but not for other bacteria including Gram negative rods and coagulase negative staphylococci. Therefore, biopsies are warranted in such situations to confirm the identity of the

causative agent. Performing blood cultures immediately following biopsy does not add any benefit [20]. In the setting of positive blood cultures for staphylococci (especially for *S. aureus*), streptococci and enterococci, clinicians should look for concurrent infective endocarditis especially in patients with valvular prosthesis or underlying valvular disease and/or new-onset heart failure [21].

Vertebral needle biopsy is usually guided by CT. But in patients for whom an immediate surgical intervention (see below) is warranted samples could be obtained via open procedure. Although open biopsy had a higher diagnostic yield than needle biopsy, a CT-guided needle biopsy of the affected bone and aspiration of abscess, if present, is proposed initially because it is less invasive [22]. The specimens should be sent for bacterial (aerobic and anaerobic), and, in some circumstances, fungal, and mycobacterial (see below) cultures and also for histologic examination and if necessary polymerase chain reaction. Retaining some sample (unfixed) is recommended in case of need for subsequent molecular diagnostic testing. If the patient is on antibiotic treatment it is usually recommended to stop it several days before performing the biopsy because prior antibiotic exposure is likely to reduce the yield. However a recent study suggests that the negative effect on microbiologic results of antibiotics administered prior to percutaneous and open biopsy cultures might be overestimated [23].

If cultures of blood and the needle aspirate are negative and the suspicion for vertebral osteomyelitis remains high performing a second biopsy is suggested [20]. Alternative investigations include percutaneous endoscopic discectomy and drainage (PEDD), or open excisional biopsy. Another alternative to be discussed is the initiation an empiric therapy [22].

Additional tests

- **Nucleic acid amplification testing** may be useful if initial aerobic and anaerobic cultures are negative in patients who have already been treated with antibiotics or are infected with

fastidious microorganisms such as *Mycobacterium tuberculosis* or *Coxiella burnetii*. Contamination with skin flora may lead to false positive results.

- **Brucella serology** should be performed in patients with clinical signs suggestive of brucellosis and/or exposed to a potential source and/or coming from endemic areas [1].
- **Cultures on specific media** for fungi or mycobacteria could be proposed for patients with epidemiologic or host risk factors [1].
- **Interferon (IFN)-γ-releasing assay** may also be performed in patients originating or residing in endemic regions or having risk factors for tuberculosis (TB). Because this test has a high sensitivity and negative predictive value (91% and 95% respectively in a recent study), it could be useful for excluding a diagnosis of active TB vertebral osteomyelitis [24].

1D Role of Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in vertebral osteomyelitis

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are two commonly measured blood markers in VO. In a retrospective series of 345 cases of proven pyogenic VO, of which 74% were bacteraemic, median CRP was 13.1 mg/dL (IQR 5.5-22.0) and ESR 77mm/hour (IQR 55-100) [25]. In another retrospective series of 440 native pyogenic VO not associated with surgery, of which 78% was bacteraemic, mean ESR was 68±31mm/hour and CRP was 13.5±9.5mg/dL [26].Similarly a study of 42 surgically treated pyogenic VO with bacteraemia in 31%, the mean ESR was 42mm/hour (range, 3-140) and CRP was 14mg/L (range, 1-29) on admission [27]. CRP can be elevated too; in a retrospective study of 40 patients with VO with 43% bacteraemia, the mean ESR was 79±27mm/hour and CRP 165±79mg/L on admission [28]. Additionally in a series of 129 patients with pyogenic VO, median CRP was significantly higher in culture-positive versus culture-negative cases (207mg/dL versus 54mg/dL) [29]. In patients with pyogenic VO, even if previously exposed to

antibiotics, open surgical biopsy or needle biopsy and higher median CRP, male gender, bacteraemia were independently associated with tissue culture positivity, but not antibiotic-free duration [30,31]. ESR and CRP have some utility in predicting treatment failure and poor outcome. An elevated CRP is associated with longer term functional disability from VO. [25,32]. .

Among a series of 40 patients, mean ESR was 85mm/hour (range, 40-145) which gradually declined to a mean of 25mm/hour by the end of antibiotic therapy and to 12mm/hour by 16 weeks. By the end of antibiotic therapy, ESR decreased to 50% of pre-treatment value in 94%, and by 16 weeks, nearly half had normal ESR [33]. More than 50% reduction in ESR from pre-treatment value in the first month, has been shown to rarely associated with failed conservative treatment [34]. In a 5-year retrospective series of 111 patients with pyogenic VO, ESR was elevated in 95% on admission. Twenty three of 24 patients (96%) less than 60 years with >25% reduction in ESR from pre-treatment value at 4 weeks did well without surgery. In contrast, 2 of 15 patients (13%) with impaired immunity and no change in ESR versus 34 of 36 patients (94%) with normal immunity and >25% reduction in ESR responded without surgery [35]. Additionally in patients with VO and bacteraemia, CRP ≥100mg/L, age ≥60 years and Charlson's comorbidity index ≥2 were independently associated with in-hospital mortality [36]. Despite all of the above CRP and ESR are non-specific markers; low values do not exclude VO, and higher values must be interpreted within the clinical context and other investigations when available.

2A Bacterial Vertebral Osteomyelitis

The epidemiology of the pyogenic native VO varies in different parts of the world according to different social, economic and geographical features: typical bacterial agents such as *Staphylococcus aureus*, streptococcal species, enteric bacteria, and other Gram-negative rods are the most common pyogenic pathogens identified in native VO [1,37]. Haematogenous spread remains the most common route of infection, preferentially affecting the lumbar (58%), thoracic (30%) and cervical

(11%) regions with multifocal involvement being relatively uncommon (4%) [4]. Indeed, the global increased incidence of VO may be partly attributed to MRSA bacteraemias which have compounded the burden of *S. aureus* bacteraemia [38]. Direct inoculation can occur following spinal surgery, instrumentation, lumbar puncture or epidural procedures. Delay in diagnosis is common, with average time to diagnosis approximately 2-4 months and initial mis-diagnosis in one third [4].

The prevalence of Gram-positive bacteria ranges from 26 to 93%: *Staphylococcus aureus* is the most common organism, Gram-negative bacilli are isolated less frequently (table 1). Bacterial VO is commonly monomicrobial, with *Staphylococcus aureus* being the predominant pathogen in 20-84% [1,4]. The diagnosis should be suspected in patients complaining of new localized neck or back pain with concomitant or recent history of *S. aureus* blood stream infection [1,4] Blood cultures can be positive in up to 50% of cases of S. aureus native VO. Obtaining a positive blood culture for S. aureus can obviate an image-guided aspiration specimen in patients with clinical, laboratory, and radiologic findings suggestive of native VO [39]. In a national Danish study including 8739 patients with *S. aureus* bloodstream infection, 6% of them were associated to native VO and were found in patients older than 50 years old without any identified obvious entry source [40]. Continuous bacteremia with the same coagulase-negative staphylococci in nephropathic patients under chronic hemodialysis with suspected native VO or in patients with infected intravascular devices may also obviate the aspiration biopsy [41,42]. *Staphylococcus lugdunensis*, which can often behave like *S. aureus*, has been associated with deep-seated infections [43]. Polymicrobial infection accounts for the 9% of the analyzed cases [37].

It is also important to consider the involvement of anaerobe species in non-pyogenic intervertebral disease. This area has received significant attention following a double-blind randomised clinical controlled trial showing the efficacy of a 100-day course of co-amoxiclav in the treatment of lower back pain and Modic type 1 changes.[44] Notwithstanding that the current evidence from clinical trials is insufficient to recommend such a long-term course of antibiotics for any group of patients

with chronic low back pain, there is abundant evidence showing colonisation of degenerated and oedematous discs by low-virulence anaerobes, such as *Cutibacterium acnes* (formerly *Propionibacterium acnes*) and coagulase-negative staphylococci [45,46] *C. acnes* can be part of the normal oral microbiota and it has been hypothesised that bloodstream invasion may occur during low-grade oral trauma events such as toothbrushing, which may be particularly relevant in the absence of other septic foci. Indeed vertebral osteomyelitis secondary to common oral infections has been reported [47]. In our own clinical experience we have encountered oral commensal streptococci, such as Streptococcus mitis, as one of the bacterial causes of VO (unpublished). Nonetheless the exact role of all commensal species in the pathophysiology of Modic changes and intervertebral disc degeneration is yet to be elucidated [46].

2B Epidemiology of brucella vertebral osteomyelitis

Brucellar Vertebral Osteomyelitis (BVO) is common in countries of the Mediterranean basin, Latin America, the Middle East, parts of Africa, and Western Asia where human Brucellosis is endemic [1,48].

In a large retrospective Spanish study conducted between 1982 and 2005, 918 patients were identified with brucella infection, of which 10.4% had vertebral localization [49]. In Turkey, Mete et al reported 100 cases of native VO between 2000 and 2007 from a single center; 24 of them had Brucella species [50]. Al Soub et al. in Qatar reported a (10.7%) incidence of BVO [51].

Grammatico et al, on the contrary, reported that BVO accounted for 0.7% of their cases in France [52]. While, Sakkas et al described the epidemiology of native VO, in a single center in central Greece from 2000–2007, Brucella etiology accounted for 34% of the cases [53]. *Brucella* spp were isolated in the blood of 37.5% and in the bone marrow of 66.7% of patients with brucellar species infection. Ten of 11 patients had IgM and IgG anti-brucella antibodies and a positive Rose-Bengal reaction. Three

patients had been diagnosed with brucellosis and treated 5 months (2 patients) and 12 months (1 patient) earlier. One of these patients had detectable IgG and IgA, but not IgM antibrucella antibodies and responded to treatment. Outside the United States, the Coombs test is commonly used for the diagnosis of brucellar native VO [araj]. Enzyme-linked immunosorbent assay (ELISA) has proven to be superior in complicated cases of brucellosis and might be of value in patients with brucellar NVO [54].

According to data reported by Colmenero, that lumbar and lumbosacral level are involved in 67% of their cases; multiple-level involvement was described as 0–9% of cases [49]. The IDSA recommends a total duration of 3 months of antimicrobial therapy for most patients with NVO due to *Brucella* spp [1]. The two most commonly used regimens include combination of streptomycin for 2–3 weeks and doxycycline for 3 months, or doxycycline and rifampin (both for 3 months). In a cohort of patients 20% experienced treatment failure, with no significant difference between patients treated with doxycycline-streptomycin and those treated with doxycycline-rifampin [49].

In conclusion, as previously reported the incidence of BVO is extremely variable in those countries where human brucellosis is highly endemic. Thus, patients with native VO from highly endemic countries, *Brucella* spp have to be considered in the differential diagnosis.

2C Fungal vertebral osteomyelitis

Fungal native VO is uncommon, ranging from 0.5-1.6% in most large case series, and associated with immunosuppression [4] as well as with intravenous drug use. In a large systematic review of reported cases from 1970 to 2011 of *Candida* osteomyelitis, 105 of 207 cases afflicted the vertebra. The commonest symptoms were local pain, tenderness and erythema in 93% with fever only in 28%. Common radiological features were bony erosion in 66%, reduced intervertebral space in 42% and extension into soft tissues and epidural abscess in 23% respectively. Median white cell count was 10,100/mm^3, ESR 92mm/hour and CRP 12mg/dL [55].

In a larger case series and literature review of 65 cases of Candida VO, 61% was associated with candidaemia with a delay of 2-12 months in 70% between onset of candidaemia and diagnosis of *Candida* VO. The most common vertebral sites were lumbar in 61%, lower thoracic 41% and multiple levels 15%. *C albicans* was responsible in 61%, *C tropicalis* 23% and *C glabrata* 9%. Antifungal therapy alone was used in 50%, surgery alone 5%, and combined antifungal therapy and surgery 45% [56].

A review of 41 cases of *Aspergillus* VO, immunocompromised status was found in 66%. Median delay in diagnosis was 12 weeks. Back pain was noted in 54% and neurological compromise in 29%. White cell count was <11,000/mm^3 in 13/18 and ESR >40mm/hour in 16/20. Lumbar vertebrae were affected in 54%, thoracic vertebrae 46%, and multiple levels 22%. *Aspergillus fumigatus* was isolated in 71%, *A nidulans* and *A flavus* in 7% each. Antifungal therapy alone was used in 29% and surgery in 71%, with overall recovery of 68% [57]. Increasingly, Aspergillus VO was reported to occur in immunocompetent patients with a more recent case series and literature review of 44 cases with predisposing conditions in 84%, presumed to be haematogenous in 62% and contiguous 30%. Fever was reported in 20%, back pain 93%, and neurological compromise 41%. Surgery was performed in 57%, and cure with antifungal therapy and surgery was 69% and antifungal therapy alone 71% [58].

2D Tuberculous vertebral osteomyelitis (TBVO)

Although uncommon in the western world, tuberculosis remains an important cause of spinal infection globally. Among patients with extrapulmonary tuberculosis, 10-15% have skeletal involvement, of which the spine is the most commonly affected site in approximately 50% [59,60]. In Europe and USA, bone and joint infections account for 2.2-4.7% of tuberculosis cases overall. In developed countries, the disease typically affects older persons above 50 years of age, reflecting perhaps reactivation of legacy, latent TB, contrasting with children and younger adults presenting with spinal tuberculosis in endemic countries [59,60].

Unlike pyogenic VO, clinical presentation is characteristically slow and insidious with duration of symptoms lasting from weeks to years, averaging 4 to 11 months prior to diagnosis. Consequently, late complications including vertebral destruction and spinal cord compression are not uncommon [5]. Chronic back pain is the most frequent complaint, usually localized to the site of involvement. In up to 61% of cases, back pain is the only symptom at presentation [59]. Constitutional symptoms, such as fever, weight loss and malaise, are present in only 20-30% of osteoarticular tuberculosis. Advanced neurological deficits such as paraplegia, tetraplegia and spinal deformities may occur in 22-76%[59,60]. Over 50% of patients will have evidence of a paraspinal abscess at the time of presentation [61]. Concomitant or reported history pulmonary tuberculosis is present in 50-75% [59,60]. On occasion, *M. tuberculosis* vertebral osteomyelitis may present with slow extension of infection into the soft tissues and ligaments, a "cold abscess". There is a notable absence of pain and other classic signs of inflammation in these instances [59].

Magnetic resonance imaging is the preferred neuroimaging modality. Spinal tuberculosis can affect any level of the spine, with predilection for the thoracic, followed by lumbar then cervical region. Whole spine screening can assess for multifocal non-contiguous involvement present in 16.3% to 71.4%[1-2]. Characteristic radiological findings are: destruction of bony vertebral bodies with relative preservation of intervertebral disc space, disruption of endplates, involvement of anterior vertebral body with sparing of the posterior arch, presence of spinal deformities and smooth walled paravertebral "cold" abscesses[1-2]. Chest X-ray may detect concomitant pulmonary tuberculosis [59,60]. In mycobacterial vertebral osteomyelitis higher uptakes levels at FDG-PET were detected in in comparison with pyogenic spondylodiscitis. PET-CT use appeared useful in the disease follow-up after treatment initiation to guide duration [17].

The paucibacillary nature of TBVO makes microbiological diagnosis challenging. Sampling of infected bone for mycobacterial culture in addition to histologic analysis is the critical factor in establishing a definitive diagnosis. The diagnostic yield for a percutaneous aspirate or CT guided biopsy is in the

range of 42 - 76%, however, the yield varies with the nature of the procedure performed [62]. Where possible, core biopsies are preferable to fine-needle aspirates [63]. Open biopsies have a greater sensitivity, however, are more invasive, they are recommended where an initial biopsy has been unsuccessful.

Radiologically guided specimens should be sent for mycobacterial smear and culture, histology and molecular testing if available. Due to the lower bacterial burden, smear positivity for acid-fast bacilli remains low, up to 52%. Mycobacterial culture is the gold standard and positive in up to 83% of cases, but results are often delayed. Nucleic Acid Amplification testing (NAAT) including polymerase chain reaction (PCR) allows rapid turnaround with reported high sensitivity and specificity. However, the sensitivity is increased where tissue microscopy is positive for mycobacteria and hence, the yield remains dependent on nature and quality of the sample, this may be limited in paucibacillary infection. Increasingly NAAT assays are able to identify resistance to rifampicin, and use of multiplex assays or whole genome sequencing may in future be able to identify other resistance markers which may obviate culture. Nonetheless, current limitations necessitate the ongoing use of conventional culture methods to obtain a phenotypic antimicrobial susceptibility.

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Histopathology is a key component of the diagnostic algorithm and often provides the first indication of tuberculosis; histology is confirmatory in approximately 60% with findings of epithelioid cell granulomas (85%), granular necrotic background (82%), lymphocytic infiltrate (76%) and multinucleated Langerhans giant cells (55%) [64,65]. However, it is noted that some biopsies may be falsely negative.

The peripheral white cell may often be normal. Gok et al. (2014) reported an elevated leukocyte count of > 10,000/mm3 in only 22% of patients compared with 47% of patients with pyogenic vertebral osteomyelitis [5]. Elevated ESR, CRP, normochromic normocytic anaemia and hypoalbuminaemia may be present. Tuberculin Skin tests (TST) and Interferon gamma release assays (IGRA) are not useful for a definitive diagnosis of TBVO. The tests may help identify patients at risk of

infection when positive. When negative, these can be used as an adjunct in excluding a diagnosis of active tuberculosis. However, either test may be negative in patients with latent or active tuberculosis, in the elderly, and also in those who are immunocompromised or immune-suppressed for other reasons [59,60]. Concurrent HIV must be diagnosed and treated.

Unlike other manifestations of tuberculosis, the evidence base for the management of TBVO relies on observational studies, particularly in relation to treatment duration. For drug susceptible *M. tuberculosis* strains, standard tuberculosis therapy is used (isoniazid, rifampicin, ethambutol and pyrazinamide for the first two months), however, the duration of isoniazid and rifampicin is often prolonged in practice. Individualised treatment is common; the total duration of therapy is typically in the range of 12-18 months [59]. Shorter treatment courses of 6-9 months are as effective and successful as 18-month regimens in trials conducted by the Medical Research Council (MRC) Working Party on Tuberculosis of the Spine[5]. The British Thoracic Society, American Thoracic Society and World Health Organisation recommend 6 months, 6-9 months and 9 months treatment respectively for spinal tuberculosis. Longer duration of therapy may be indicated in patients on regimens not containing rifampicin, extensive or advanced disease and multi drug resistant (MDR) TB. If there is evidence of central nervous system involvement, including an epidural abscess, pre-emptive use of steroids to prevent the development of a paradoxical inflammatory reaction should be considered.

In ambulatory patients, there was no additional benefit of surgical debridement with good response in 82-95% on medical treatment alone[5]. However, surgery would still be indicated in patients failing to respond to conservative therapy, new or worsening neurological complications and mechanical instability from vertebral destruction or kyphosis. Of note, it is estimated that surgical intervention may be required in around 16% of patients with MDR TB despite maximal pharmacological therapy [66]. In addition, a propensity for relapse in patients with undrained secondary psoas abscesses is described. Hence, percutaneous drainage should be considered early in patients with large collections and those who are judged to have a poor clinical response to antimicrobial therapy [61].

Response to therapy can be difficult to gauge; assessment relies on gradual improvement in clinical parameters including pain scores, mobility, increase in body weight, and recovery of neurological deficits [61]. Serial imaging performed within the first six months of treatment will often suggest disease progression; hence, progress MRIs are not useful in monitoring response to therapy. However, progress MRIs remain necessary in patients who do not demonstrate expected clinical improvement [59,61].

3A Antibiotic treatment of Bacterial (Pyogenic) VO

Most published guidance has previously recommended 6 – 12 weeks of typically intravenous antibiotic treatment for a pyogenic discitis. The 2015 IDSA guidance shortens this to 6 weeks, moreover emphasising the role for oral antibiotics with high oral bioavailablity in addition to intravenous options. These guidelines recommend the prompt initiation of an empiric antibiotic treatment in patients with VO only in patients with neurological compromise and when signs of sepsis or hemodynamic instability are present [1]. Otherwise, when clinical conditions are stable and no signs of neurological involvement are present, the prescription of an antibiotic treatment should be postponed aiming to achieve a microbiological diagnosis. A 6-week course of parenteral or highly bioavailable oral antimicrobial therapy is currently recommended for patients with pyogenic spondylodiscitis, with prolonged antibiotic courses suggested only when *Brucella* is involved [1]. Antibiotic options for the treatment of spondylodiscitis according with etiology are summarized in Table 2.

Many new antimicrobials with specific activity against gram-positive pathogens, including resistant isolates, have been recently introduced in routine clinical practice. Among these, dalbavancin and tedizolid represent investigational and interesting options for the treatment of vertebral osteomyelitis. Dalbavancin is a new parenteral lipoglycopeptide and is characterized by a prolonged half-life, allowing a single-dose infusion for the treatment of skin and soft tissue infections [67]. Dalbavancin possess a good bone penetration and has been recently found to be effective and well

tolerated at the dose of 1500 mg on days 1 and 8 for the treatment of osteomyelitis in adults [68]. Tedizolid is a new oxazolidinone and is currently approved for the treatment of acute bacterial skin and soft tissue infections. Advantages of tedizolid versus linezolid are the longer *in vivo* half-life allowing a once daily administration and the lower risk of myelotoxicity and drug – drug interactions with selective serotonin reuptake inhibitors and other compounds with serotonergic activity [69]. A phase 2 study investigating tolerability, safety and efficacy of tedizolid for the treatment of bone and joint infections is currently recruiting (NCT030090459).

The vast majority of studies on antibiotic duration are retrospective, observational studies. A single prospective open labelled randomised trial from France in adults demonstrated non-inferiority of 6 weeks duration of antibiotic treatment duration for microbiologically confirmed (positive blood culture or disc biopsy) discitis compared to 12 weeks [70].. Notably a high proportion (44%) of patients were treated with predominantly oral antibiotics; with 52% of patients overall receiving intravenous treatment for less than 14 days in a non-standardised fashion. However, the authors report non-inferiority of 6-week regimes in the elderly (aged >75 years); patients with immunocompromise or diabetes, endocarditis or neurology, possibly due to power limitations. Restrictions in patient selection which may limit generalisability of these results are: exclusion of patients with a vertebral implant; those with no microbiological confirmation and those with fungal, Brucella or mycobacterial infection. Authors report a higher risk of treatment failure, regardless of duration, in patients aged >75yrs and those with *S. aureus* infection.

In relation to this pathogen, a single cohort retrospective study of antibiotic treatment of methicillin-sensitive *Staphylococcus aureus* discitis in adults from Sheffield, UK, found similar outcomes in those receiving ≤12 weeks treatment compared to those receiving >12 weeks treatment, with no difference between those who received ≤4 weeks or >4 weeks intravenous antibiotics [71]. Infection due to MRSA, undrained paravertebral or psoas abscesses and end-stage renal disease were identified as independent risk factors for recurrence in a retrospective study by Park *et al*., and a

prolonged course of antibiotic treatment (≥ 8 weeks) was associated with a lower risk of recurrence compared with standard treatment duration (6-8 weeks) among high-risk patients presenting at least one risk factor for recurrence [72].

A number of studies have provided evidence to support the use of oral antibiotics in treatment of VO. In the study by Bernard et al [70]a high proportion (44%) of patients were treated with predominantly oral antibiotics; with 52% of patients overall receiving intravenous treatment for less than 14 days in a non-standardised fashion. The results from the OVIVA study [73] , a recently published multi-centre, randomised, open-label trial of initial 6 week intravenous versus oral antibiotic in osteomyelitis and bone infection, including VO patients, found non-inferiority with oral treatment. A retrospective study in VO patients managed surgically [74] reported non-inferiority of short (<3 week) intravenous antibiotic courses, followed by 4 week oral treatment versus long (>3 week) intravenous antibiotic courses in patients with VO with a low risk of recurrence; this was not the case in those with high risk of recurrence (risk factors: paraspinal abscess and/or positive blood culture). There is also one, intriguing, Turkish study [75]reporting success with a shorter, 4-week, course of intravenous antibiotic combined with hyperbaric oxygen treatment in post-microsurgical discectomy discitis with no oral continuation treatment. However, there are study limitations in terms of low microbiological confirmation rate, lack of therapeutic drug monitoring and absence of a comparator group.

Although risk factors for treatment failure and recurrence are not well established and no algorithms for the identification of high-risk patients are currently available, prolonged antibiotic treatment courses might probably be considered case by case based on patient's risk factors, particularly when source control is not timely performed.

3B Indications for surgery

Surgical intervention is indicated when patients develop progressive loss of motor and/or neurological functions, cauda equina syndrome, progressive deformities or spinal instability. Failure of antibiotic therapy, as evidenced by persistent pain or systemic inflammation/ infection may also lead to surgical intervention [1,2]. Surgical management consists of debridement of all purulent and granulation tissue, sequestered bone and bone that is compressing neural structures [3].

An area of controversy is the optimal timing of surgery that most benefits the patient. Prior studies report conflicting findings. While some authors have found an advantage to earlier surgical intervention, others have not been able to show benefit [3]. All these studies are limited. They are typically small, retrospective and from a single center.

A study by Segreto, et al. evaluated the outcomes of early (less than 24 hours) versus delayed surgical treatment of VO using a large nationwide inpatient database [3]. This study found that VO patients who underwent surgery after 24 hours of admission had higher likelihood of morbidity and mortality. Unfortunately, an analysis such as this using a large health care database is not able to identify or control for confounding variables.

The optimal approach for the surgical management of VO is controversial and guided by clinical judgment and the experience of the surgeon. While an anterior approach allows better exposure for debridement and reconstruction, it may be more technically difficult than a posterior approach.

Also controversial is use of instrumentation in patients with active infection, the benefit of one-stage versus two-staged procedures, and the use of autograft versus allograft.

Nonetheless, several studies suggest favorable outcomes and low recurrent infection rates using instrumentation in the surgical treatment of spinal infection [2].

In summary, surgical treatment options for VO are varied and the selection of approach and procedure should be tailored to the individual patient's circumstances, in the absence of high-quality evidence to make more specific recommendations.

Conclusion

The review highlights key points related to diagnostic and therapeutic aspects in VO as well as important areas for future studies and research as there are still many unknowns with regards to:

1) What is or are the most effective investigations/ technique for spinal biopsies and impact of these on clinical outcome and cost effectiveness of therapy?

2) Is finding aetiology affects patient's outcome?

3) Is outcome better with or without surgery and what is the best time for surgery if this is clinically indicated?

High quality studies and trails to guide empirical and tailored therapy for specific aetiologies within the above generic guidance are recommended.

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Table 1. Comparative features and incidence of bacterial causes of vertebral osteomyelitis

Microbiology*	Incidence	Route of infection
Staphylococcus aureus	20%-84%	Most common pathogen. 1.7% to 6% blood stream infection complicated by vertebral osteomyelitis
Coagulase-negative Staphylococci	5%-16%	Device related bacteraemia or direct inoculation in post-operative infections
Streptococci Enterococci	5%-20%	Haematogenous spread. Associated with infective endocarditis in 26%
Enterobacteriaceae	7%-33%	Haematogenous spread from urinary tract infections in older population. Commonly *E. coli, Proteus, Klebsiella, Enterobacter spp*.
Anaerobes	<4%	Contiguous spread from pelvic or intraabdominal foci. *Propionibacterium acnes* direct inoculation from implants
Polymicrobial	<10%	Contiguous spread

Table 2: Antimicrobial treatment options for spondylodiscitis*

Etiology	Intravenous treatment options	Oral treatment options	Investigational treatment options
Methicillin-susceptible staphylococci	Oxacillin, flucloxacillin or nafcillin (2 g every 4-6 h, or by continuous infusion) or Ceftriaxone (2g every 12 h) or Cefazolin (8-12 g every 24 h, continuous infusion)	Levofloxacin (500 mg every 12 h) + rifampin (10 mg/kg/day)	Moxifloxacin (400 mg every 24h) or Dalbavancin (1500 mg on day 1 and 8) or Tedizolid (200 mg every 24 h)
Methicillin-resistant staphylococci	Teicoplanin or Vancomycin**(use locally agreed dosage according to renal function) or Daptomycin (10 mg/kg/day)	Linezolid (600 mg every 12 h)	Dalbavancin (1500 mg on day 1 and 8) or Tedizolid (200 mg every 24 h)
Enterococci (penicillin-susceptible)	Ampicillin (3-4 g every 6 h)	Linezolid (600 mg every 12 h)	Dalbavancin (1500 mg on day 1 and 8) or Tedizolid (200 mg every 24 h)
Enterococci (penicillin-resistant or allergy to penicillins)	Teicoplanin or Vancomycin**(use locally agreed dosage according to renal function) or Daptomycin (10-12 mg/kg/day)	Linezolid (600 mg every 12 h)	Dalbavancin (1500 mg on day 1 and 8) or Tedizolid (200 mg every 24 h)
Streptococci	Ampicillin (3-4 g every 6 h) or Ceftriaxone (2 g every 24 h) or Teicoplanin or Vancomycin**(use locally agreed dosage according to renal function) or Daptomycin (10 mg/kg/day)	Amoxicillin (1 g every 6 h) or Linezolid (600 mg every 12 h)	Moxifloxacin (400 mg every 24h)
Gram-negative pathogens	According to sensitivities Ceftazidime (2 g every 6-8 h) or Meropenem (2 g every 8 h)	Ciprofloxacin (750 mg every 12 h) or Levofloxacin (500 mg every 12 h)	--

*Please follow local guidance and/ or local sensitivity pattern and/ or advice from your local infection specialists

**consider therapeutic drug monitoring, when available