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Hot Topic

Hot topics on vertebral osteomyelitis from the International Society of Antimicrobial Chemotherapy

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1. Introduction

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 or 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. The 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, neurological deficits, septicaemia and mortality (mortality rate range 4–29%). VO is typically treated with antibiotics, but up to 40–50% of VO patients may eventually require surgical intervention [1–3].

Despite advances in diagnostic modalities as well as medical and surgical care, there are still many controversial areas with

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regard both to diagnostic and therapeutic strategies in VO. In this review, a number of 'hot topics' on VO were selected and reviewed by members of the Bone and Skin & Soft Tissue 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 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.

2. Clinical findings and investigations

2.1. Clinical findings of vertebral osteomyelitis

VO is clinically characterised by pain along the spinal area affected with or without fever. Focal back or neck pain is relatively common, occurring in most 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 and percussion of the affected area and is 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 aetiology 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 localised spinal pain and muscle spasm. Extension of infection posteriorly into the epidural space leads to worsening back pain with radiculopathy, 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 neurological signs in the lower limbs, and palpation for distended bladder. Abscess of the cervical spine is characterised by cervical rigidity, dysphagia or torticollis. Abscess of the lumbar spine can spread through the ischiatic foramen and involve the gluteus muscles. When lower lumbosacral roots are involved, 'cauda syndrome' can appear. Sinus formation can be the result of a long-standing unrecognised infection [8].

Symptoms may be more non-specific in children, including irritability, limping gait, hip pain, refusal to crawl, sit or walk, and abdominal pain and incontinence may even 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, occurring in only about one-half of patients. It is uncommon in mycobacterial, brucellar or fungal VO and may be masked in patients receiving therapy with analgesics with antipyretic effects. However, fever is common in older children with VO. Cervical infection, tuberculous vertebral osteomyelitis (TBVO) and late diagnosis are often associated with systemic symptoms of weight loss, weakness and anorexia [1,4,5].

2.2. Imaging for vertebral osteomyelitis

Plain radiographs are often normal in the early phases, and abnormal findings are usually not apparent before 3 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].

Computed tomography (CT) findings of VO appear earlier than those seen on plain radiographs. The main abnormalities include endplate irregularities. CT is especially useful for detecting bony sequestrum and soft tissue abscess and to exclude epidural abscess [10]. CT can also be useful for guiding vertebral biopsies. CT remains the first-line alternative test when magnetic resonance imaging (MRI) is not available or is unfeasible [1].

MRI is the most sensitive imaging test for confirming the diagnosis of VO [10]. Abnormalities are often detected earlier on MRI than on CT. Typical MRI findings include (i) decreased signal intensity in the vertebral bodies and disc and loss of endplate definition (T_1-weighted images), (ii) increased disc signal intensity and/or increased vertebral body signal intensity (T_2-weighted images) and (iii) contrast enhancement of the vertebral body and disc. Multisequence 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 only be proposed for patients whose clinical status has not improved at the planned time for discontinuation of antibiotics in order to evaluate 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 labelled technetium is neither sensitive nor specific enough for the diagnosis of VO. 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 with 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 h to complete, necessitating multiple visits to the nuclear medicine department.
- Labelled leukocyte scan is not recommended for the diagnosis of VO owing to poor sensitivity and specificity values.
- Positron emission tomography (PET) using fluorine-18-fluorodeoxyglucose (^{18}F-FDG), combined with CT: during recent years, many studies investigating the potential role of ^{18}F-FDG-PET/CT 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 ^{18}F-FDG-PET/CT 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 recently been reported for ^{18}F-FDG-PET/CT compared with MRI (95% and 88% for ^{18}F-FDG-PET/CT vs. 85% and 66% for MRI, respectively) [14,15]. However, false positives have been attributed to tumour, degenerative spinal disease and/or spinal implants. Moreover, ^{18}F-FDG-PET/CT has been associated with a higher diagnostic value compared with MRI for the detection of early spondylodiscitis within 2 weeks after symptoms onset [16]. Another important advantage of ^{18}F-FDG-PET/CT over MRI is represented by the identification of metastatic foci of infection, especially in patients with bacteraemia, allowing prompt source control [14]. Conversely, MRI is more sensitive than ^{18}F-FDG-PET/CT for evaluation of soft tissue involvement and for identification of small epidural abscess [14]. Of note, ^{18}F-FDG-PET/CT 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 to the aetiology of infection [13]. Specifically, higher uptake values have been reported in tuberculous spondylodiscitis compared with pyogenic spondylodiscitis [17].

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

2.3. Microbiological investigations for vertebral osteomyelitis

The cornerstone for microbiological diagnosis is specimen culture obtained from a biopsy. A microbiological diagnosis should be obtained to target antimicrobial treatment. However, in special circumstances, including neurological compromise and sepsis, prompt empirical antibiotic therapy is warranted. In patients with clinical, biochemical and imaging studies suggesting VO with positive blood cultures for *Staphylococcus aureus* or *Staphylococcus lugdunensis*, biopsies have not been shown to add additional diagnostic value [1].

Blood cultures (at least two sets, with aerobic and anaerobic bottles) are recommended. 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. However, in patients for whom immediate surgical intervention (see below) is warranted, samples could be obtained via open procedure. Although open biopsy has a higher diagnostic yield than needle biopsy, CT-guided needle biopsy of the affected bone and aspiration of the abscess, if present, is proposed initially because it is less invasive [22]. Specimens should be sent for bacterial (aerobic and anaerobic) and, in some circumstances, fungal and mycobacterial (see below) cultures and also for histological examination and, if necessary, PCR. Retaining some sample (unfixed) is recommended in case of a need for subsequent molecular diagnostic testing. If the patient is receiving 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 suggested that the negative effect of antibiotics administered prior to percutaneous and open biopsy cultures on microbiological results might be overestimated [23].

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

Additional tests

- Nucleic acid amplification testing (NAAT) may be useful if initial aerobic and anaerobic cultures are negative in patients who have already been treated with antibiotics or who are infected with fastidious micro-organisms 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 epidemiological or host risk factors [1].
- Interferon-gamma (IFNγ)-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 TBVO [24].

2.4. Role of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in vertebral osteomyelitis

ESR and 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, the median CRP was 13.1 mg/dL [interquartile range (IQR) 5.5–22.0 mg/dL] and the median ESR was 77 mm/h (IQR 55–100 mm/h) [25]. In another retrospective series of 440 native pyogenic VO not associated with surgery, of which 78% were bacteraemic, the mean ESR was 68 $\pm$ 31 mm/h and the mean CRP was 13.5 $\pm$ 9.5 mg/dL [26]. Similarly, a study of 42 surgically-treated pyogenic VO cases, with bacteraemia in 31%, the mean ESR was 42 mm/h (range 3–140 mm/h) and the mean CRP was 14 mg/L (range 1–29 mg/L) on admission [27]. CRP can also be elevated; in a retrospective study of 40 patients with VO, with 43% bacteraemia, the mean ESR was 79 $\pm$ 27 mm/h and the mean CRP was 165 $\pm$ 79 mg/L on admission [28]. Moreover, in a series of 129 patients with pyogenic VO, the median CRP was significantly higher in culture-positive versus culture-negative cases (207 mg/dL vs. 54 mg/dL) [29]. In patients with pyogenic VO, even if previously exposed to antibiotics, open surgical biopsy or needle biopsy, higher median CRP, male sex and 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, the mean ESR was 85 mm/h (range 40–145 mm/h), which gradually declined to a mean of 25 mm/h by the end of antibiotic therapy and to 12 mm/h by 16 weeks. By the end of antibiotic therapy, the ESR decreased to 50% of the pre-treatment value in 94% of cases, and by 16 weeks nearly one-half had a normal ESR [33]. A greater than 50% reduction in ESR from the pre-treatment value in the first month has been shown to rarely be 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. Of 24 patients aged $<$60 years with a $>$25% reduction in ESR from pre-treatment value at 4 weeks, 23 (96%) did well without surgery. In contrast, 2 (13%) of 15 patients with impaired immunity and no change in ESR versus 34 (94%) of 36 patients with normal immunity and a $>$25% reduction in ESR responded without surgery [35]. In addition, in patients with VO and bacteraemia, CRP $\geq$ 100 mg/L, age $\geq$60 years and Charlson comorbidity index $\geq$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.

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

Microbiology[a]	Incidence (%)	Route of infection
Staphylococcus aureus	20–84	Most common pathogen; 1.7–6% of bloodstream infections complicated by VO
Coagulase-negative staphylococci	5–16	Device-related bacteraemia or direct inoculation in post-operative infections
Streptococci and enterococci	5–20	Haematogenous spread. Associated with infective endocarditis in 26%
Enterobacteriaceae	7–33	Haematogenous spread from urinary tract infections in older population. Commonly *Escherichia coli, Proteus, Klebsiella, Enterobacter* spp.
Anaerobes	<4	Contiguous spread from pelvic or intra-abdominal foci. *Cutibacterium acnes* direct inoculation from implants
Polymicrobial	<10	Contiguous spread

[a] Adapted from [1,37].

3. Some causes of vertebral osteomyelitis

3.1. Bacterial vertebral osteomyelitis

The epidemiology of pyogenic native VO varies in different parts of the world according to different social, economic and geographical features: typical bacterial agents such as *S. aureus, Streptococcus* spp., 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 methicillin-resistant *S. aureus* (MRSA) bacteraemia, which has 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 an average time to diagnosis of approximately 2–4 months and initial misdiagnosis in one-third [4].

The prevalence of Gram-positive bacteria ranges from 26–93% (*S. aureus* is the most common organism), whereas Gram-negative bacilli are isolated less frequently (Table 1). Bacterial VO is commonly monomicrobial, with *S. aureus* being the predominant pathogen in 20–84% [1,4]. The diagnosis should be suspected in patients complaining of new localised neck or back pain with concomitant or recent history of *S. aureus* bloodstream infection [1,4]. Blood cultures can be positive in up to 50% of *S. aureus* native VO cases. Obtaining a positive blood culture for *S. aureus* can obviate an image-guided aspiration specimen in patients with clinical, laboratory and radiological findings suggestive of native VO [39]. In a national Danish study including 8739 patients with *S. aureus* bloodstream infection, 6% were associated with native VO and were found in patients older than 50 years without any obvious entry source identified [40]. Continuous bacteraemia with the same coagulase-negative staphylococci in nephropathic patients under chronic haemodialysis 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 9% of analysed cases [37].

It is also important to consider the involvement of anaerobic 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 amoxicillin/clavulanic acid 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]. *Cutibacterium 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, VO 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 data). None the less, the exact role of all commensal species in the pathophysiology of Modic changes and intervertebral disc degeneration is yet to be elucidated [46].

3.2. Epidemiology of brucellar vertebral osteomyelitis (BVO)

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 1982–2005, 918 patients were identified with *Brucella* infection, of which 10.4% had vertebral localisation [49]. In Turkey, Mete et al. reported 100 cases of native VO between 2000–2007 from a single centre, of which 24 had *Brucella* spp. infection [50]. Al Soub et al. reported a 10.7% incidence of BVO in Qatar [51].

In contrast, Grammatico et al. reported that BVO accounted for 0.7% of cases in France [52]. Sakkas et al. described the epidemiology of native VO in a single centre in central Greece from 2000–2007, where *Brucella* aetiology accounted for 34% of cases [53]. *Brucella* spp. were isolated in the blood of 37.5% and in the bone marrow of 66.7% of patients with *Brucella* spp. infection. Ten of eleven patients had anti-brucella IgM and IgG 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, anti-brucella antibodies and responded to treatment. Outside of the USA, the Coombs test is commonly used for the diagnosis of native BVO [54]. Enzyme-linked immunosorbent assay (ELISA) has proven to be superior in complicated cases of brucellosis and might be of value in patients with native BVO [54].

According to data reported by Colmenero et al., the lumbar and lumbosacral level are involved in 67% of cases; multiple-level involvement was described in 0–9% of cases [49]. The IDSA recommends a total duration of 3 months of antimicrobial therapy for most patients with native VO 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 rifampicin both for 3 months. In a cohort of patients, 20% experienced treatment failure with no significant difference between patients treated with doxycycline/streptomycin or doxycycline/rifampicin [49].

In conclusion, as previously reported, the incidence of BVO is extremely variable in those countries where human brucellosis is highly endemic. Thus, for patients with native VO from highly en-

demic countries, *Brucella* spp. have to be considered in the differential diagnosis.

3.3. Fungal vertebral osteomyelitis

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

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

In a review of 41 cases of *Aspergillus* VO, immunocompromised status was found in 66%. The median delay in diagnosis was 12 weeks. Back pain was noted in 54% and neurological compromise in 29%. The WBC count was <11 000/mm^3 in 13/18 and the ESR was >40 mm/h in 16/20. The lumbar vertebrae were affected in 54%, the thoracic vertebrae in 46% and multiple levels in 22%. *Aspergillus fumigatus* was isolated in 71% and *Aspergillus nidulans* and *Aspergillus flavus* in 7% each. Antifungal therapy alone was used in 29% and surgery in 71%, with overall recovery of 68% [57]. Increasingly, *Aspergillus* VO is 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 in 30%. Fever was reported in 20%, back pain in 93% and neurological compromise in 41%. Surgery was performed in 57%, and cure with antifungal therapy and surgery was 69% and with antifungal therapy alone was 71% [58].

3.4. Tuberculous vertebral osteomyelitis (TBVO)

Although uncommon in the Western world, TB 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 the USA, bone and joint infections account for 2.2–4.7% of TB cases overall. In developed countries, the disease typically affects older persons >50 years of age, reflecting perhaps reactivation of legacy, latent TB, contrasting with children and younger adults presenting with spinal TB in endemic countries [59,60].

Unlike pyogenic VO, clinical presentation is characteristically slow and insidious with the duration of symptoms lasting from weeks to years, averaging 4–11 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 localised 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 TB. 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]. A concomitant or reported history of pulmonary TB is present in 50–75% [59,60]. On occasion, *M. tuberculosis* VO 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].

MRI is the preferred neuroimaging modality. Spinal TB can affect any level of the spine, with a predilection for the thoracic, followed by lumbar then cervical region. Whole-spine screening can assess for multifocal non-contiguous involvement present in 16.3–71.4%. 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. Chest radiography may detect concomitant pulmonary TB [59,60]. In mycobacterial VO, higher uptake levels on ^{18}F-FDG-PET are detected in comparison with pyogenic spondylodiscitis. Use of PET-CT appears useful in disease follow-up after treatment initiation in order to guide duration [17].

The paucibacillary nature of TBVO makes microbiological diagnosis challenging. Sampling of infected bone for mycobacterial culture in addition to histological 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 they are more invasive and 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. Owing to the lower bacterial burden, smear positivity for acid-fast bacilli remains low (up to 52%). Mycobacterial culture is the gold standard and is positive in up to 83% of cases, but results are often delayed. Nucleic acid amplification testing (NAAT) including PCR allows a 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 the nature and quality of the sample, which 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 that may obviate culture. None the less, current limitations necessitate the ongoing use of conventional culture methods to determine phenotypic antimicrobial susceptibility.

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

The peripheral WBC count may often be normal. Eren Gök et al. reported an elevated leukocyte count of >10 000/mm^3 in only 22% of patients compared with 47% of patients with pyogenic VO [5]. Elevated ESR and CRP, normochromic normocytic anaemia and hypoalbuminaemia may be present. Tuberculin skin tests and interferon-gamma release assays 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 TB. However, either test may be negative in patients with latent or active TB, in the elderly as well as in those who are immunocompromised or immunosuppressed for other reasons [59,60]. Concurrent human immunodeficiency virus (HIV) infection must be diagnosed and treated.

Unlike other manifestations of TB, 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 TB therapy is used (isoniazid, rifampicin, ethambutol and pyrazinamide for the first 2 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 were as effective and successful as 18-month regimens in trials conducted by the Medical Research Council Working Party on Tuberculosis of the Spine. The British Thoracic Society, the American Thoracic Society and the World Health Organization (WHO) recommend 6 months, 6–9 months and 9 months of treatment, respectively, for spinal TB. A longer duration of therapy may be indicated in patients receiving regimens not containing rifampicin, with extensive or advanced disease, and with multidrug-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. However, surgery would still be indicated in patients failing to respond to conservative therapy, with new or worsening neurological complications, and with mechanical instability from vertebral destruction or kyphosis. Of note, it is estimated that surgical intervention may be required in approximately 16% of patients with MDR-TB despite maximal pharmacological therapy [66]. In addition, a propensity for relapse in patients with undrained secondary psoas abscess is described. Hence, percutaneous drainage should be considered early in patients with large collections and in 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 6 months of treatment will often suggest disease progression; hence, progress MRI is not useful in monitoring response to therapy. However, progress MRI remains necessary in patients who do not demonstrate expected clinical improvement [59,61].

4. General management of vertebral osteomyelitis

4.1. Antibiotic treatment of bacterial (pyogenic) vertebral osteomyelitis

Most published guidance has previously recommended 6–12 weeks of typically intravenous (i.v.) antibiotic treatment for pyogenic discitis. The 2015 IDSA guidance shortens this to 6 weeks, moreover emphasising the role of oral antibiotics with high oral bioavailability in addition to i.v. options. These guidelines recommend the prompt initiation of empirical antibiotic treatment in patients with VO only in patients with neurological compromise and when signs of sepsis or haemodynamic instability are present [1]. Otherwise, when clinical conditions are stable and no signs of neurological involvement are present, prescription of 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 to aetiology are summarised 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 VO. Dalbavancin is a new parenteral lipoglycopeptide and is characterised by a prolonged half-life, allowing single-dose infusion for the treatment of skin and soft-tissue infections [67]. Dalbavancin possesses good bone penetration and has recently been found to be effective and well tolerated at a 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 skin-structure infections. Advantages of tedizolid versus linezolid are the longer in vivo half-life allowing 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 the tolerability, safety and efficacy of tedizolid for the treatment of bone and joint infections is currently recruiting (NCT03009045).

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 for microbiologically confirmed (positive blood culture or disc biopsy) discitis compared with 12 weeks [70]. Notably, a high proportion (44%) of patients were treated with predominantly oral antibiotics, with 52% of patients overall receiving i.v. treatment for <14 days in a non-standardised fashion. However, the authors reported non-inferiority of a 6-week regimen in the elderly (age >75 years) and in patients with immunocompromise, diabetes, endocarditis or neurology, possibly due to power limitations. Restrictions in patient selection that may limit the generalisability of these results are the exclusion of patients with a vertebral implant, those with no microbiological confirmation, and those with fungal, *Brucella* or mycobacterial infection. The authors report a higher risk of treatment failure, regardless of duration, in patients aged >75 years and those with *S. aureus* infection.

In relation to this pathogen, a single retrospective cohort study of antibiotic treatment of methicillin-susceptible *S. aureus* discitis in adults from Sheffield (UK) found similar outcomes in those receiving ≤12 weeks of treatment compared with those receiving >12 weeks of treatment, with no difference between those who received ≤4 weeks or >4 weeks of i.v. 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 a 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 the treatment of VO. In a study by Bernard et al., a high proportion (44%) of patients were treated with predominantly oral antibiotics, with 52% of patients overall receiving i.v. treatment for <14 days in a non-standardised fashion [70]. The results from the OVIVA study [73], a recently published multicentre, randomised, open-label trial of initial 6-week i.v. versus oral antibiotics in osteomyelitis and bone infection, including VO patients, found non-inferiority with oral treatment. A retrospective study in VO patients managed surgically reported non-inferiority of short (≤3 weeks) i.v. antibiotic courses followed by 4 weeks of oral treatment versus long (>3 weeks) i.v. antibiotic courses in patients with VO with a low risk of recurrence; this was not the case in those with a high risk of recurrence (risk factors of paraspinal abscess and/or positive blood culture) [74]. There is also one, intriguing, Turkish study reporting success with a shorter, 4-week course of i.v. antibiotics combined with hyperbaric oxygen treatment in post-microsurgical discectomy discitis with no oral con-

Table 2
Antimicrobial treatment options for spondylodiscitis[a].

Aetiology	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 (2 g every 12 h) or cefazolin (8–12 g every 24 h, continuous infusion)	Levofloxacin (500 mg every 12 h) + rifampicin (10 mg/kg/day)	Moxifloxacin (400 mg every 24h) or dalbavancin (1500 mg on Days 1 and 8) or tedizolid (200 mg every 24 h)
Methicillin-resistant staphylococci	Teicoplanin or vancomycin[b] (use locally agreed dosage according to renal function) or daptomycin (10 mg/kg/day)	Linezolid (600 mg every 12 h)	Dalbavancin (1500 mg on Days 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 Days 1 and 8) or tedizolid (200 mg every 24 h)
Enterococci (penicillin-resistant or allergy to penicillins)	Teicoplanin or vancomycin[b] (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 Days 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[b] (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 susceptibility: 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)	–

[a] Follow local guidance and/or local susceptibility pattern and/or advice from local infection specialists.
[b] Consider therapeutic drug monitoring, when available.

tinuation treatment [75]. 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 patients' risk factors, particularly when source control is not performed in a timely manner.

4.2. 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. Whilst some authors have found an advantage to earlier surgical intervention, others have not been able to show a benefit [3]. All of these studies are limited; they are typically small, retrospective and from a single centre.

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

The optimal approach for the surgical management of VO is controversial and is guided by clinical judgement and the experience of the surgeon. Whilst an anterior approach allows better exposure for debridement and reconstruction, it may be more technically difficult than a posterior approach. Also controversial is the use of instrumentation in patients with active infection, the benefit of one-stage versus two-staged procedures, and the use of autograft versus allograft.

None the less, several studies suggest favourable 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.

5. 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 regard to the following:

(1) What is/are the most effective investigations/techniques for spinal biopsies and the impact of these on clinical outcome and cost effectiveness of therapy?
(2) Does finding the aetiology affect patient outcome?
(3) Is the outcome better with or without surgery and what is the best time for surgery if this is clinically indicated?
(4) High-quality studies and trials to guide empirical and tailored therapy for specific aetiologies within the above generic guidance are recommended.

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