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Vertebral osteomyelitis in adults: an update

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Abstract

Introduction: The incidence of vertebral osteomyelitis is increasing, attributed to an ageing population with inherent co-morbidities and improved case ascertainment.

Sources of data: References were retrieved from the PubMed database using the terms 'vertebral osteomyelitis' and 'spondylodiscitis' between January 1, 2009 and April 30, 2014 published in English as checked in May 2014 (>1000 abstracts checked).

Areas of agreement: Blood cultures and whole spine imaging with magnetic resonance imaging are essential investigations. Thorough debridement is the mainstay of surgical management, although placing metalwork in active infection is becoming increasingly common.

Areas of controversy: The extent of pursuing spinal biopsies to determine aetiology, antimicrobial choices and duration, monitoring the response to treatment, and surgical techniques and timing all vary widely in clinical practice with heterogeneous studies limiting comparisons. Surgery, rather than conservative approaches, is being proposed as the default management choice, because it can, in carefully selected patients, offer faster reduction in pain scores and improved quality of life.

Areas timely for developing research: Further studies are needed to define the most effective technique for spinal biopsies to maximize determining aetiology. High-quality trials are required to provide an evidence base for both the medical and surgical management of vertebral osteomyelitis, including challenging medical management as the default option.

Key words: vertebral osteomyelitis, spondylodiscitis, diagnosis, management

Introduction

Vertebral osteomyelitis (VO) describes an infection of the vertebrae and intervertebral disc and is also known as spondylodiscitis. By comparison, discitis describes infection limited to the intervertebral disc; however, there are many who consider discitis and VO as different stages of the same disease process.[1] The aetiology can be pyogenic (bacterial),

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granulomatous (tuberculous, brucellar, fungal) or parasitic. VO can arise from haematogenous seeding, contiguous spread from infection in adjacent soft tissues or direct inoculation during spinal surgery or procedures, e.g. epidural. Infections of spinal metalwork following surgery can occur early (within 1 month) or late (>1 month). The incidence of VO is increasing: incidence increased from 2.2 to 5.8 per 100 000 person-years over 1995–2008 in Denmark, with an average adjusted annual increase of 7%;[2] and incidence increased from 5.3 to 7.4 per 100 000 population per year over 2007–10 in Japan.[3] This has been attributed to an ageing population with inherent co-morbidities, and improved case ascertainment, particularly related to the widespread use of magnetic resonance imaging (MRI).[2,3] The incidence was 9.8/100 000 per year in New Zealand for those aged >65[4] and was highest in the elderly (>70 years) in Denmark.[2] The incidence of specific causes of VO has also significantly increased: *Staphylococcus aureus* from 1.6 to 2.5 cases per 100 000 person-years (1995–2008),[2] streptococcal species by +0.009/100 000 population per year (1991–2011)[5] and culture negative by +0.059/100 000 population per year (2005–09)[6] or +0.009/100 000 population per year (1991–2011).[5]

Epidemiology

Pyogenic VO (PVO) is more common in older patients, mean age 59–69 years, and has a male preponderance, males accounting for 52–69% patients, from large studies (≥100 PVO cases)[2,3,7–10] and pooled data.[11] Tuberculous VO (TVO) affects a broader span of ages, mean age 27–76 years from pooled worldwide data,[12] reflecting the younger patients seen in developing countries and the bimodal distribution in developed countries, the first peak 20–40 years being immigrants and human immunodeficiency virus (HIV) co-infected patients and the second peak 60–80 years being immunosuppressed and ageing patients with co-morbidities.[13] TVO can be significantly more common in female patients than PVO[3,14] or not,[15,16] and there is a wider spectrum from pooled worldwide data, males 36–73%.[12] Like PVO, brucellar VO (BVO) occurs in older patients, mean age 53–58 years, but is perhaps more equally distributed between the sexes, males 41–63%.[15–20] Fungal cases are much rarer, but a review of 83 *Aspergillus* VO cases found median age 49 years and male predominance, 71%.[21]

Predisposing factors for PVO are reported to include diabetes mellitus, immunosuppression, renal failure, malignancy, heart disease, liver cirrhosis, alcohol excess, intravenous drug use (IVDU), HIV infection, spinal surgery and instrumentation, preceding bacteraemia and hence the risk factors for that e.g. intravascular devices, rheumatoid arthritis and malnutrition.[2,3,7,9–11] Inevitably, the prevalence of these risk factors can vary widely according to the population studied: IVDU occurred in 2–79% patients in the pooled data;[11] and rates of diabetes mellitus range 10–37% in large studies.[2,3,7,9] In addition to these co-morbidities, rates of post-procedural VO are increased by prolonged operation time, instrumentation, posterior surgical approach, extensive soft tissue dissection and/or devitalization, creation of dead space, repeat surgery, surgery through previously irradiated tissue, excess blood loss, blood transfusions and emergency surgery.[22–24] TVO is predictably more common in high prevalence countries or immigrants from such countries.[12,25] Furthermore, diabetes mellitus, chronic renal failure, IVDU and immunosuppression including corticosteroids and HIV, as well as previous and concurrent tuberculosis are risk factors for TVO.[12–14] The additional specific risk factors for BVO, beyond those for PVO, include consumption of unpasteurized dairy products, animal husbandry, livestock farming, and meat industry, abattoir, veterinarian, healthcare and laboratory workers in endemic areas.[16–18,20,26] The most important risk factor for fungal VO is immunosuppression, congenital or acquired, and prior orthopaedic surgery is common, 19%.[21]

Clinical characteristics

VO can be a notoriously difficult diagnosis to make, even more so in resource-poor settings. This challenge arises from the combination of the relative rarity of

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the disease, the much higher incidence of non-specific back pain in the general population, the protean presentation, the non-pathognomonic imaging and the variable rate of positivity from cultures. The most common clinical characteristic of VO is undoubtedly back pain regardless of aetiology accounting for 67–100% patients from large studies (≥100 VO cases)[2,7,8,14,15,27] and pooled data[11,12] but fever is much less frequent, 2–60%,[2,7,8,11,12,14,15,27] and mostly absent with *Propionibacterium acnes*.[28] Without significant fever, a non-specific insidious illness does not necessarily prompt the instigation of spinal imaging and relevant cultures unless there is a high index of suspicion. Since the majority of VO results from haematogenous seeding of an infection, the initial symptoms and signs are often dominated by the primary infection site, such as urinary tract or skin and soft tissue. Bacteraemias due to *S. aureus* and streptococcal species are prone to cause metastatic infections, including VO; metastatic infection was seen in 73% patients with one or more risk factors and 41% had no localizing signs or symptoms.[29] Diagnostic delay is a recurrent theme throughout studies of VO, and this inevitably has consequences on developing more extensive infection and hence complications. A further consideration is that the delay in considering VO as a diagnosis may determine how classical, or extensive, the radiological appearance is and the development of abscesses from which there is a greater chance of identifying the causative organism.

There may be features in the clinical presentation that suggest the aetiology, e.g. TVO has a significantly more indolent course than PVO and is frequently associated with active tuberculosis in other organs;[14] neurological sequelae are more common in TVO secondary to epidural abscesses and greater bony destruction often as a result of diagnostic delay;[13,30] and abscesses, such as epidural and paravertebral, are more common with methicillin-sensitive *S. aureus* (MSSA) than Gram-negative bacteria (GNB).[31] BVO and TVO often present sub-acutely, and in countries endemic for both infections, this can be particularly challenging. A study from Turkey evaluating BVO ($n = 96$), TVO ($n = 63$) and PVO ($n = 55$) concluded that TVO and BVO remained the leading causes of VO with delayed diagnosis, and that the clinical predictors of BVO were sweating, arthralgias and hepatomegaly.[16] A further study from Turkey comparing BVO ($n = 30$) versus non-BVO ($n = 50$) of which 17 were TVO found that BVO was significantly associated with lower Charlson co-morbidity scores, higher rates of constitutional symptoms and fever, lower inflammatory markers and higher values for haemoglobin, total protein and albumin.[19] Nonetheless, white cell count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are not sufficiently discriminatory to aid in determining aetiology reliably. Although there are classical stereotypes of Gram-negative PVO after abdominal or genitourinary procedures, polymicrobial PVO secondary to decubitus ulcers, TVO in immigrants from high prevalence countries and fungal VO in heavily immunosuppressed patients, there have been many clinical surprises reported in the literature over the last 5 years, e.g. *Aspergillus* VO following oral and inhaled steroids for COPD as the only immunosuppression,[21] VO due to non-tuberculous mycobacteria even in immunocompetent patients,[32] PVO without any back pain[33] and *Salmonella* VO in patients without sickle cell disease or immunocompromise.[34] This reinforces that a high index of suspicion for VO may be required to make the diagnosis, and an open mind kept regarding the aetiology.

Confirming the aetiology

The mainstays of diagnosis are spinal imaging and spinal biopsy material for microbiological testing and ideally histopathology. In any infectious disease, it is always preferable to confirm the aetiology before treatment, but this has particular relevance in VO given the length of treatment required and the increasing morbidity and mortality of delayed effective treatment.[13,35–37] Although *S. aureus* is the most common cause (42–58%),[2,10,11,37,38] the diversity of potential causative organisms is illustrated in Table 1, emphasizing the importance of pursuing investigations to determine the aetiology. Additionally, increasing antimicrobial resistance rates make identifying the causative organism and its susceptibilities ever more essential.

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Table 1 Causative organisms in case reports and large studies (>100 PVO cases) published between January 1, 2009 and April 30, 2014

More common causes (from large studies)	
Bacteria	
Gram positive	Gram negative
Staphylococcus aureus	*Escherichia coli*
Staphylococcus epidermidis	*Pseudomonas aeruginosa*
Streptococcus sp.	*Proteus mirabilis*
Enterococcus sp.	
Less common causes (from case reports)	
Bacteria	
Abiotrophia adiacens	
Acinetobacter	
Actinobaculum schaalii	
Aerococcus urinae	
Arcanobacterium haemolyticum	
Bacteroides fragilis	
Balantidium coli	
Bartonella henselae/quintana	
Brucella melitensis	
Burkholderia cepacia/pseudomallei	
Campylobacter coli/fetus/jejuni	
Capnocytophaga canimosus	
Cellulomonas	
Citrobacter koseri	
Clostridium difficile	
Corynebacterium striatum	
Eggerthella lenta	
Eikenella corrodens	
Enterobacter aerogenes/cloacae	
Enterococcus faecalis/faecium	
Erysipelothrix rhusiopathiae	
Fusobacterium nucleatum/varium	
Gardnerella vaginalis	
Gemella haemolysans/morbillium	
Granulicatella adiacens	
Haemophilus influenzae/parainfluenzae	
Kingella kingae	
Klebsiella pneumoniae	
Kytococcus schroeteri	
Lactobacillus	
Lactococcus garvieae	
Nocardia brasiliensis	
Parvimonas micra	
Pasteurella multocida	
Propionibacterium acnes	
Prevotella oralis	
Salmonella enteritidis/typhi	
Serratia marcescens	
Staphylococcus haemolyticus/saccharolyticus/simulans/xylosus	
Streptobacillus moniliformis	
Streptococcus bovis/equi/milleri/mutans/oralis/pneumoniae/pyogenes/suis/tigurinus/viridans/ Group B *Streptococcus*	
Treponema pallidum	
Tropheryma whipplei	
Veillonella	
Yersinia enterolytica	
Mycobacteria	
Mycobacterium tuberculosis	
Mycobacterium abscessus/avium complex/bovis/chelonae/fortuitum/heckeshornense/xenopi	
Mycobacterium leprae	
Fungi/moulds	
Aspergillus flavus/fumigatus/nidulans	
Blastoschizomyces capitatus	
Candida albicans/dubliniensis/glabrata/krusei/lusitaniae/parapsilosis/sake	
Coccidioidomycosis	
Cryptococcus	
Fusarium falciforme	
Geotrichum capitatum	
Scedosporium apiospermum/prolificans	
Parasites	
Echinococcus multilocularis	

Blood cultures

There is consensus that blood cultures should be taken for all patients with suspected VO. However, the rate of positive blood cultures varies 40–89%[6,10,11,14,35,38–43] and likely relates to prior antibiotic therapy, the relative ease of culturing the causative organism, the concentration of organisms in the bloodstream, local epidemiology and the pathogenesis of VO (haematogenous or not). Bone marrow culture increases the yield for BVO: blood culture 37.5% versus bone marrow 66.7%[43]

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or by 15–20%.[36] Ascertaining bacteraemia in the preceding year may help determine the aetiology.[10]

Spinal biopsy cultures

Most authors agree that a radiologically guided biopsy constitutes best practice if an open biopsy during surgery is not indicated or other cultures have not yielded the diagnosis. The material needs to be set up for aerobic, anaerobic, mycobacterial and fungal cultures. Most commonly, computed tomography (CT) or fluoroscopic guidance is used, but MRI-guided biopsy has been described[44] and endoscopy[45,46] is increasing. CT-guided biopsies are performed in preference to fluoroscopy due to more accurate localization, multiplanar views, the ability to differentiate necrotic bone and solid lesions, and not exposing the operator to ionizing radiation.[47] A meta-analysis comparing fluoroscopic-guided and CT-guided percutaneous biopsies found slightly higher rates of adequacy and accuracy with CT-guided biopsies and less complications, but these were not significant with the numbers involved.[48] The rate of diagnosis from percutaneous biopsies for microbiology in PVO varies 14–76%[6,10,15,27,35,47,49,50] and in TVO is 42–76%,[13] both reflecting the heterogeneity of studies. Open biopsies have a significantly higher rate of positive cultures than percutaneous biopsies: 91 versus 53% ($P < 0.001$)[51] and 93 versus 48% ($P = 0.003$),[39] respectively, but greater associated morbidity.[13,42,47] The newer minimally invasive percutaneous endoscopy procedures offer both a diagnostic and therapeutic capacity and could be beneficial as a study of percutaneous endoscopic discectomy and drainage versus CT-guided biopsies for diagnostic purposes reported positive cultures in 90 versus 47%, respectively,[52] but their role in routine clinical practice needs to be determined.

Multiple biopsy sampling is more controversial. Some feel that either multiple samples taken at the outset to increase the yield of organisms[45] or a second biopsy, either repeat percutaneous or open biopsy, performed in the absence of a microbiological diagnosis post-blood cultures and first spinal biopsy,[36,42,46,53] is not justified.[6,54] A study of second percutaneous biopsies found no significant improvement in yield.[55] Complications are more likely with repeated sampling.[42,47] A study of post-biopsy blood cultures reported them being of limited value.[55] A new technique for increasing yield from spinal sampling has been trialled involving injecting saline and collecting the reflux using either 1 or 2 needles, which resulted in 91.6% cultures being positive.[56] Prior antimicrobial therapy undoubtedly diminishes the positivity of blood cultures, but the effect on biopsy culture is less clear: two studies report no significant association,[6,51] whereas others found a significantly lower diagnostic rate,[49,57] with ≥4 days of prior antibiotic exposure significantly decreasing culture growth.[57]

Histology

Histology should be performed routinely. The histological changes of VO include inflammatory cell infiltration, vascular proliferation associated with granulation tissue, fibrosis, thrombosed blood vessels and bone necrosis depending on the stage of disease, and infective organisms may be identified.[15,50] The rate of diagnosis from histology of spinal biopsy material is reported as 56–82%[15,47,50] for PVO and TVO. Even in the context of previous or concurrent malignancy, new spinal lesions may represent infection rather than metastases: 200 cases radiologically consistent with malignancy found that 5% biopsies were culture positive.[50]

Polymerase chain reaction assays

A broad range 16S rDNA polymerase chain reaction (PCR) assay directly on percutaneous biopsy tissue was more sensitive than conventional culture for PVO, particularly with prior antimicrobial exposure,[58] although careful interpretation is needed when possible skin contaminants are identified. The major disadvantage is the lack of susceptibility data. The sensitivity is lower than culture for TVO, so specific *Mycobacterium tuberculosis* PCR assays are recommended for suspected TVO.[58] Multiplex real-time PCRs to distinguish brucellosis and tuberculosis performed on vertebral tissue successfully diagnosed 10/11 BVO and 10/12 TVO[59] and 14/15 samples.[60]

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Serology

BVO may be diagnosed from serological tests using the standard tube agglutination test titre >1:160[17,26] or >1:320[18] with suggestive clinical signs and symptoms, or serum antibody concentration 4-fold rise in serum samples after 2- to 3-week intervals.[17,18,26] Negative *Brucella* serology occurring with positive cultures demonstrates that negative serology does not necessarily exclude the diagnosis.[61] In potential fungal cases, antigen detection tests on blood can be useful, e.g. mannan, galactomannan and cryptococcal antigen for *Candida albicans*, *Aspergillus* and *Cryptococcus*, respectively.[36]

Imaging for diagnosis

As back pain is not universally present in VO and non-contiguous infection can occur, it is best practice to image the whole spine. A study of cervical VO described concomitant non-contiguous infection in another region of the spine in 47% patients.[62] There are a plethora of modalities for imaging the spine, each offering differing qualities.

Magnetic resonance imaging

Currently, MRI is the imaging modality of choice for potential VO due to its high sensitivity and specificity, including in early disease; the ability to evaluate the extent of disease encompassing soft tissues, bony and neural structures; and the lack of ionizing radiation.[63] The early changes of PVO, namely inflammatory oedema and increased blood flow, are seen as reduced signal on T_1-weighted spin echo (SE) images and increased signal on T_2-weighted fat-saturated (better than T_2-weighted SE) images of the vertebral bodies and discs, with post-contrast fat-suppressed T_1-weighted sequences particularly able to contrast hyperaemic and normal bone and surrounding soft tissues.[63] In very early disease, the changes may only be subtle end plate oedema and dehydrated disc more suggestive of degeneration that then evolves into more typical features of infection[64] or may involve only a single vertebral body.[65] If the clinical suspicion is high, then a repeat MRI between 8 and 22 days later is suggested.[64] The classic description for PVO is an infected intervertebral disc with the two adjacent vertebrae affected and destruction of the vertebral end plates, the latter manifesting as ill-defined vertebral end plates, and the lumbar spine is most commonly affected.[63] The addition of gadolinium contrast improves the accuracy of MRI, especially in early disease.[53,64] Extension of the infection to involve the epidural space can result in epidural abscesses or epidural phlegmon, which with contrast can be distinguished as diffuse homogenous enhancement of phlegmon compared with the rim enhancement surrounding a non-enhancing centre of an abscess.[63]

TVO typically involves the thoracolumbar spine and is characterized by adjacent vertebral infection, which spares the intervertebral disc, anterior vertebral collapse that can lead to gibbus formation, multifocal non-contiguous vertebral infection resulting from subligamentous extension of infection, paraspinal and psoas abscesses, meningeal involvement, and thecal sac displacement and/or spinal cord compromise.[63,66,67] The abscesses, thecal sac displacement and meningeal involvement are best seen on post-contrast fat-suppressed T_1-weighted images.[63] While all these features favour TVO rather than PVO, calcification of large paraspinal abscesses effectively seals the diagnosis. Thoracic involvement and ≥3 spinal levels affected make TVO significantly more likely than PVO.[14] However, there is a spectrum of imaging findings and cases may not be obviously tuberculous on MRI, as e.g. single vertebral involvement and infection affecting the posterior vertebral elements are described.[63]

In BVO, affected vertebrae and intervertebral discs have low T_1-weighted and high T_2-weighted signal intensities in the acute phase, and low T_1-weighted and heterogenous T_2-weighted signal intensities in the subacute and chronic phases. At all phases, the T_2-weighted fat-saturated images have high signal intensities.[68] A study of 25 patients with BVO found that diffusion-weighted images were 100% accurate in differentiating the acute and chronic phases as hyperintense and hypointense, respectively.[68] However, it was not possible to reliably differentiate the subacute cases. Typically, the anterior superior end plate is the initial focus of infection, and as the infection progresses, the whole vertebral body is affected with

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subsequent spread to the intervertebral disc and then adjacent vertebral body. Although reported as rare, the study mentioned earlier observed 28% patients had non-contiguous multifocal involvement.[68] Features considered characteristic for BVO include vertebral end plate defects mimicking intraosseous disc herniation, loss of muscle fat borders, paraspinal granulation tissue and gas within the intervertebral disc. Since vertebral collapse, gibbus formation, paravertebral and epidural abscesses, and spinal cord compression are rare with BVO, these are deemed to distinguish between TVO and BVO,[68,69] although paravertebral and/or epidural abscesses have been reported in 32–44% patients[68,69] and spinal cord compression in 40% patients.[68] The lumbar spine is predominantly involved in BVO.[17,20,69]

Aspergillus VO is typically seen as low T_1-weighted and high T_2-weighted signal intensities with gadolinium contrast enhancement of T_1-weighted images, and the most common findings were spinal cord compression, epidural and paraspinal abscesses, spondylolisthesis and decreased intervertebral space.[21] Fungal VO has also been described as showing a lack of hyperintense T_2-weighted signal within the intervertebral disc.[36]

The combination of reduced signal T_1-weighted images with increased signal T_2-weighted images is also seen in degenerative disc disease and known as Modic 1 change; given the predilection of VO for older age, this is an important differential diagnosis. However, diffusion-weighted MRI can distinguish these two disease processes as Modic 1 change in degenerative disc disease gives hypointense images and VO gives hyperintense images.[70] Additionally, the vertebral end plates are preserved in degenerative disc disease in contrast to VO.[63]

Computed tomography

CT is better than MRI for evaluating cortical bone involvement and has its niche in the assessment of sequestra and pathological calcification.[53,63] Abscesses in the paraspinal tissues can be demonstrated well on CT with characteristically a thick nodular rim pre-contrast and rim enhancement post-contrast around low attenuation fluid. Calcification of a multi-loculated, rim-enhancing paraspinal abscess in association with vertebral body destruction would be classical for TVO as opposed to PVO.[63] CT perfusion can distinguish TVO and neoplasms.[71] In clinical practice, CT is most commonly used for image-guided biopsies.

Single-positron emission computed tomography

Single-positron emission computed tomography (SPECT) is a three-dimensional imaging involving an injectable radionuclide, in contrast to the two-dimensional images obtained from a nuclear medicine bone scan. In studies comparing SPECT versus bone scans, SPECT had higher sensitivity and specificity[72] and detected 30% more solitary spinal lesions including due to VO.[73]

^{18}F-fluorodeoxyglucose positron emission tomography

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) is a three-dimensional imaging technique involving the radiopharmaceutical ^{18}F-FDG, which has increased uptake in metabolically active tissues including in the setting of infection. A meta-analysis of ^{18}F-FDG-PET as a diagnostic tool for VO found that from the 12 eligible studies involving a total of 224 patients, the sensitivity was 97%, specificity 88% and with a pretest probability over 50%, the positive predictive value was 0.96 and negative predictive value 0.85.[74] It can distinguish Modic 1 changes from PVO.[75] Combined PET/CT scanners afford better localization and can overcome artefacts from implants so, where available, are likely to play a beneficial role in diagnostic uncertainty.[74] A study comparing ^{18}F-FDG-PET and MRI for VO diagnosis concluded that they showed similar accuracy, 75 versus 81%, respectively, and therefore, ^{18}F-FDG-PET could be used when diagnostic doubt remained after MRI or MRI was unavailable.[76] In BVO, ^{18}F-FDG-PET detected additional spinal lesions as well as soft tissue and epidural foci of infection compared with MRI.[77]

Bone scans (scintigraphy)

Bone scans are nuclear medicine scans involving a labelled tracer, which can be ^{99m}Tc, ^{67}Ga, or

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Table 2 Recommendations for specific intravenous antibiotic choices for identified common causes of PVO from pooled reviews[42,53,79]

Common causative organisms	Intravenous antibiotic suggestions
Staphylococcus aureus, methicillin sensitive	Flucloxacillin/oxacillin/nafcillin 2 g every 6 h or Ceftriaxone 2 g once daily or Cefazolin 1–2 g every 8 h
Staphylococcus aureus, methicillin resistant	Vancomycin 15–20 mg/kg every 8–12 h to achieve adequate trough levels, i.e. 15–20 mg/l or Teicoplanin 12 mg/kg once daily after loading to achieve adequate trough levels, i.e. 20–60 mg/l or Daptomycin at least 6 mg/kg lean body weight once daily
Streptococci	Benzylpenicillin 2.4 g every 6 h or Penicillin G 5 million units every 6 h or Ceftriaxone 2 g once daily
Enterobacteriaceae	Ciprofloxacin 400 mg every 12 h* or Ceftriaxone 2 g once daily or Meropenem 1 g every 8 h or Imipenem 500 mg every 6 h
Pseudomonas aeruginosa	Ceftazidime 2 g every 8 h ± aminoglycoside or Cefepime 2 g every 8 h ± aminoglycoside or Piperacillin–tazobactam 4.5 g every 6–8 h ± aminoglycoside or Meropenem 1 g every 8 h ± aminoglycoside or Imipenem 500 mg every 6 h ± aminoglycoside
Anaerobes	Clindamycin 300–600 mg every 6–8 h† or Gram negative, e.g. *Bacteroides*: metronidazole 500 mg every 8 h or Gram positive, e.g. *Propionibacterium acnes*: ceftriaxone 2 g once daily or Penicillin G 5 million units every 6 h

Adult doses for normal renal function given.
*As good bioavailability, more likely to be given as 750 mg every 12 h orally.
†As good bioavailability, the dose may be given orally.

autologous radiolabelled white cells, giving two-dimensional images and are generally performed in three phases for detecting infection. These phases are 'angiographic' assessing increased blood flow, 'blood pool' looking for inflammation of the soft tissues and 'later/bone' evaluating bone turnover, and increased uptake in all phases is suggestive of infection.[78] There are drawbacks with each of the potential tracers: autologous white cells undergo physiological uptake into active bone marrow, ^{67}Ga is significantly taken up in the liver, bowel, bone marrow and at post-surgical sites and ^{99m}Tc is affected by bone remodelling.[78] The high sensitivity of ^{99m}Tc means a negative scan effectively excludes the diagnosis.[78] These scans are less commonly used now where alternatives are available.

Medical management

The aims of medical management are to cure the infection and prevent relapse, restore function and control pain. There are no randomized control trial (RCT) data to inform the choice of antimicrobial therapy specifically for VO. The use of dual antimicrobial therapy, especially for *S. aureus*, has not been specifically addressed in the VO literature over the period of this review. Empirical treatment must cover *S. aureus*, as the most common cause, and is otherwise determined by local epidemiology and patient risk factors. Ideally, the causative organism is identified and susceptibilities known facilitating an appropriate choice of antimicrobial, according to local treatment guidelines. Table 2 gives recommendations from the literature for specific intravenous

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antibiotic choices for the more common causes of PVO once identified. Traditionally, treatment for PVO has involved an extended course of intravenous antibiotic therapy followed by a maintenance course of oral therapy, but in recent years, there has been a move towards early oral antibiotic therapy and/or outpatient parenteral antibiotic therapy as a result of patient choice and pressure on hospital beds. Antibiotics with good bioavailability, such as clindamycin and ciprofloxacin, are ideally suited for earlier oral therapy. A retrospective study of 11 patients with *Salmonella* VO treated with 12-week ciprofloxacin either entirely orally or first 2-week intravenous showed that all had excellent to good functional outcomes.[34] A possible exception to this may occur in patients with VO due to *Pseudomonas aeruginosa* in whom intravenous therapy, with an agent other than ciprofloxacin, may be given initially to reduce the bacterial burden before switching to oral ciprofloxacin is recommended as maintenance therapy, to reduce the risk of developing resistance. High-dose levofloxacin (500 mg every 12 h) plus rifampicin 600 mg daily (both orally) has been successfully used as empirical treatment in 48 patients with PVO, in a setting with low fluoroquinolone resistance among staphylococci and enterobacteriaceae.[80] With increasing antimicrobial resistance rates worldwide, susceptibility testing becomes ever more pertinent.

Duration

Traditionally, a prolonged course of antimicrobial therapy is prescribed for VO; however, there is a wide variation in clinical practice over the length of intravenous therapy and the total length of antimicrobial treatment. Published data on successful outcomes with shorter treatment courses are accumulating. A retrospective analysis of 61 patients with PVO, excluding concomitant endocarditis, spinal implant infections or surgical wound site infections, from 2000 to 2010 reported a 97% cure rate for short intravenous (median 2.7 weeks) and overall treatment courses (median 8.1 weeks) alongside abscess drainage if required (48% patients).[81] While higher relapse rates have been significantly associated with shorter (<8 weeks) treatment courses for methicillin-resistant *S. aureus* (MRSA)[82] and GNB,[31] this has not been the case for MSSA,[82,83] although the heterogeneity of antibiotic regimes and treatment length limits drawing many conclusions. To date, there has been only one RCT that has examined the duration of antimicrobial therapy specifically for VO,[84] and although after the dates of the literature review, it has been included given its significance. This open-label, non-inferiority RCT of 6-weeks versus 12-weeks antibiotic treatment for PVO involving 351 patients from November 2006 to March 2011 found 6 weeks to be non-inferior for the proportion cured at 1 year, and no significant difference in adverse events.[84] The length of intravenous therapy was not standardized, but there was no significant difference in treatment failure rates between those receiving short (<1 week) and protracted (>1 week) intravenous therapy, and 52% received <14 days.[84]

Newer agents

The newer agents used, although not licensed, for PVO include linezolid, daptomycin, tigecycline and telavancin, all of which are active against Gram-positive bacteria including MRSA. Linezolid is bacteriostatic for staphylococci and enterococci but bactericidal for streptococci and has adequate bone penetration in human studies. However, its major limitation for use in VO is adverse drug reactions with prolonged courses, which are mostly reversible but the peripheral neuropathy can persist beyond 2 years in 75% patients.[85] Therefore, while not a first-line recommendation, its excellent oral bioavailability is advantageous when intravenous treatment is refused or not possible. Daptomycin is a concentration-dependent bactericidal agent requiring dosing at ≥6 mg/kg for osteomyelitis, with the minimum serum concentrations being the most significant predictor of creatinine kinase elevation[85] hence the preference for once daily dosing. Daptomycin has been successfully substituted when adequate vancomycin trough levels have been difficult to achieve or renal function has deteriorated with vancomycin therapy.[85,86] As daptomycin is generally well tolerated, with increasing clinical use it is likely to become a mainstay of first-line treatment particularly for MRSA. Tigecycline is bacteriostatic and is additionally active against some GNB and anaerobes. The data on bone penetration are very

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limited and differ between animal and human studies; also there are concerns about increased mortality in severe infections so, pending more data, tigecycline is a last resort choice.[85] However, a report of eight cases of post-operative VO treated with tigecycline monotherapy ($n = 4$) or in combination ($n = 4$) after failing therapy with other antibiotics, used empirically ($n = 3$) or following antibiotic susceptibility testing ($n = 5$), described successful outcomes in the seven patients with follow-up, and no relapse of infection after 1 year.[87] Telavancin is bactericidal with the same spectrum of activity as vancomycin but minimum inhibitory concentration two to eight times lower; and a single study in rabbits found good bacterial clearance despite low bone penetration.[85] Telavancin at 10 mg/kg has been used successfully in two reported cases of MRSA VO and a third case resolved infection but had renal complications.[85] Poor outcomes have particularly been associated with reduced baseline renal function. More clinical data are needed to determine its role.

Non-PVO

There are treatment guidelines covering TVO[88–90] and *Candida* VO.[91] A comprehensive review of *Aspergillus* osteomyelitis recommends surgical decompression and debridement combined with voriconazole for VO.[21] Across all *Aspergillus* osteomyelitis cases reviewed, there was no significant benefit of combination therapy over monotherapy with surgery, whereas without surgery there was a non-significant trend favouring two agents; and overall response rates were similar for amphotericin B, itraconazole and voriconazole.[21] A multicentre study of 293 patients with BVO comparing treatment with doxycycline 200 mg daily plus rifampicin 600 mg daily with or without either streptomycin, gentamicin or ciprofloxacin; or doxycycline plus streptomycin found no significant difference between the options in uncomplicated or complicated cases.[20] Patients successfully treated with combination therapy including an aminoglycoside had significantly longer treatment courses in complicated cases, median 20 versus 12 weeks ($P = 0.001$).[20] Prolonged (>6 months, median 48 weeks) treatment with triple combination antibiotics was successfully used in 18 patients with BVO to prevent any relapses or treatment failures.[92]

Monitoring

The response to treatment is generally assessed by clinical picture, monitoring CRP and ESR, and imaging. In the retrospective analysis of 61 patients treated with shorter antibiotic courses, the only independent predictor of early switch to oral antibiotics was a lower CRP at 2 weeks compared with baseline, odds ratio (OR) 0.7 per 10 mg/l increase in CRP ($P = 0.041$).[81] In a study of 45 patients with PVO, ESR >55 mm/h and CRP >2.75 mg/dl (>27.5 mg/l) at fourth week of antibiotic administration had a significantly higher risk of treatment failure (OR 5.15, $P = 0.037$) by receiver operating characteristic curve analysis.[93] MRI is frequently used to monitor progress in PVO[94] and BVO,[18] because with appropriate treatment, the increased signal on T_2-weighted fat-saturated images resolves, but the high sensitivity for detecting these changes may result in the normalization of images lagging behind the clinical improvement.[63] Bone marrow oedema and increased T_2-weighted signal in the disc can still be seen on 6-month follow-up MRI scans.[41] Although the increase back to normal in signal of T_1-weighted images has been reported to correlate well with the clinical recovery.[63] Resolution of marrow oedema and paravertebral collections as well as replacement of vertebral body marrow with fat (increase in T_1-weighted SE images) and loss of enhancement with gadolinium are seen in healed TVO.[66] Worsening vertebral body and disc enhancement and ongoing loss of vertebral disc height do not necessarily represent treatment failure and can accompany clinical improvement.[53] However, continued bone destruction on follow-up imaging should prompt a review of the diagnosis and treatment.[63] In those settings with ready availability to ^{18}F-FDG-PET imaging, it stands to play a greater role in monitoring, because ^{18}F-FDG-PET can quantify inflammatory change[78] and is able to discriminate residual and non-residual infection after treatment.[95] It has been shown to be more accurate and more specific than MRI in treatment evaluation, 86 versus 62% and 82 versus 17%, respectively;[76] and complementary to MRI in monitoring treatment response in BVO.[77] A study comparing FDG-PET and CRP determined that responders to conservative treatment were better

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identified by FDG-PET.[96] ^{18}F-FDG-PET is an essential part of a published multi-disciplinary management algorithm.[97]

Adjuncts

Spinal bracing is very commonly employed from the outset, or following a period of bed rest, for several months.[37,42,46,94,98] A study of rigid spinal bracing versus percutaneous posterior screw-rod instrumentation and a soft brace found no significant difference in infection resolution or healing times but significantly faster recovery, lower pain scores and improved quality-of-life scores in the surgically treated patients.[99] A single study has proposed adjunctive hyperbaric oxygen therapy for patients with significant co-morbidities predisposing to poor healing.[100]

Surgical management

The indications for surgery in VO are (i) failure to respond to antimicrobial therapy/source control, (ii) neurological impairment or deterioration, (iii) spinal instability or deformity that may result in intractable pain, (iv) epidural abscesses and paraspinal abscesses (certainly ≥2.5 cm) and (v) significant vertebral destruction or impending fractures.[42,45] It therefore follows that the aims of surgical management are to address the indications by (i) obtaining tissue for microbiological and/or histological assessment and thoroughly debriding the infected tissues including removal of prosthetic material if necessary, (ii) decompressing the neural structures, (iii) spinal fixation with or without instrumentation, (iv) drainage of abscesses and (v) spinal instrumentation with or without autologous bone grafting. There is no consensus on the timing of surgery, beyond emergency decompression of epidural abscesses when loss of motor or sensory function results. A study in HIV co-infected patients reported no increase in the risk of surgical complications, even with a low mean CD4 count, so concluded that HIV should not affect the decision over whether to operate,[101] although being HIV positive was significantly associated with treatment failure on bivariable analysis in an analysis of risk factors for treatment failure in VO requiring instrumentation.[102]

Debridement and defect reconstruction

Meticulous and radical debridement of infected tissues is an agreed mainstay of surgical management, so the successful outcomes from the study where no debridement was performed and metalwork sited[103] are perhaps surprising. Since VO predominantly affects the anterior vertebral elements, an anterior approach to debridement is generally preferred where possible and this is much more commonly undertaken in the cervical spine due to the additional risks of the surgical approach to the anterior thoracolumbar spine.[42,54] The options for surgical reconstruction of the debrided defects include bone grafts or titanium mesh cages to further stabilize the spine.[42,45,54,104] Titanium mesh cages are increasingly being used in preference for stabilizing the spine and correcting the spinal alignment as the titanium cage seems to resist bacterial adherence better than other metals,[54,104] avoids the morbidity of bone harvesting[45,104–106] and provides good early mechanical strength[45,104] but longer term may not be so beneficial mechanically.[45] In comparison to bone grafting, titanium mesh cages have resulted in higher fusion rates and better sagittal alignment in cervical TVO.[106] Subsistence has been shown to occur more frequently and earlier with bone grafting than cage usage.[8] For large defect reconstruction, expandable titanium cages have been successfully employed and possess intra-operative advantages of sagittal correction.[107]

Metalwork in active infection

An interesting shift in practice is the placement of metalwork for fixation during the active infection,[36,104,105] with a literature review analysis summarizing that among differing surgical approaches, avoiding metalwork placement at the site of infection or placing metalwork at the debrided site does not appear to significantly influence the outcome.[105] This review calculated that the rate of infection recurrence for instrumentation in active infection

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was <2%, which is comparable to instrumentation in non-infected spinal surgery.[105] An analysis of risk factors for treatment failure in VO requiring instrumentation found that the use of rifampicin or chronic courses of suppressive antibiotics did not significantly affect the treatment failure rate.[102] Additionally, treatment failures occurred within the first year, so the benefit of suppressive antibiotics in this setting for >1 year is likely to be minimal.[102]

Surgical approaches and staged surgery

There is much debate over the surgical approaches, 1- or 2-stage surgery and the use of and positioning of instrumentation in both PVO and TVO. To an extent, this reflects the variability of individual patients in terms of disease burden, pattern of infection, co-morbid profile and physiological reserve for surgery as well as the preferences of different surgeons. Anterior or anterolateral approaches have been used to access the spine from C1/2 through until L4/5 and been sufficient alone without needing to add posterior fixation, especially now titanium cages offer much better reconstruction than bone grafts.[54] A posterior approach is mainly used for epidural abscesses,[42,45] but anterior debridement and pedicle screw fixation have been performed from this approach.[104] An open posterior approach with instrumentation may result in a higher rate of wound infections due to the devitalization of paraspinal musculature surrounding the implanted metalwork during the surgical approach.[105] Nonetheless, long posterior fixation has been used effectively to prevent destabilization after posterior decompression.[103] Single-stage surgery for both PVO and TVO can achieve the surgical aims with less operative time, less complications, less blood loss, earlier mobilization and shorter hospital stays,[104,105,108] whereas two-stage surgery can allow recovery time between operations, which may be essential in less fit patients, and incremental instrumentation.[8,98,105] Hence, the variability of patient factors and the multiple surgical options available mean that increasingly, a patient-centred surgical plan is uniquely developed to suit each case.

Instrumentation

Anterior fixation devices enhance stability and allow earlier mobilization and rehabilitation but may not be adequate in stabilizing the spine to prevent late deformity, especially in conjunction with osteoporosis. When combined with posterior fusion, this completes circumferential fusion and restores stability to both the anterior and posterior columns.[108] Performing the posterior stabilization first has been employed by some surgeons to facilitate more radical anterior debridement[45] and to avoid contamination of the posterior field.[109] In some cases, additional posterior spinal instrumentation for fixation is indicated particularly for kyphotic deformities and when there is greater bony destruction.[42,98] Posterior instrumentation utilizing pedicle screws with hooks or hooks alone should preferentially be performed in patients with an osteoporotic spine and pedicle screws alone reserved for younger patients with better bone quality.[103] In the absence of anterior support due to the infection, posterior fixation is best undertaken two levels above and two levels below the lesion to provide greater posterior fixation and maintenance of the corrected kyphotic angle, especially in osteoporosis.[103] In cervical PVO, when corpectomy is necessary for adequate debridement, then stabilization from posterior, rather than anterior, is recommended to prevent serious complications.[62] Pedicle screw fixation gives immediate stability to the spine thereby reducing the need for bed rest and bracing.[108] A study of primary spinal stabilization showed that this facilitated nursing care and earlier mobilization, thereby avoiding the morbidity of protracted bed rest and resulted in significantly improved pain scores.[103] A study of treatment with percutaneous posterior screw-rod instrumentation and a post-operative soft brace versus rigid bracing in single-level PVO found no significant difference in resolution of the infection, but improvement in pain scores and quality of life were significantly better in the surgical group,[99] perhaps challenging the default option for conservative management of less severe cases. In the *Aspergillus* VO review, surgery was needed in the majority of cases (77%) and six cases were managed with surgery

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alone.[21] Surgery in this context involved debridement, bone grafting, stabilization, fusion and spinal cord decompression, particularly as 47% patients developed spinal cord compression secondary to epidural abscesses.

Minimally invasive surgery

Most surgery is still open, but minimally invasive surgical techniques such as percutaneous endoscopic discectomy and drainage offer combined diagnostic and therapeutic management and reduce the need for open surgery, which is particularly advantageous in older patients with co-morbidities as is commonplace in VO.[52] Also, percutaneous discectomy and drainage with fluoroscopy guidance provided good combined diagnostic and therapeutic management in post-operative intervertebral discitis.[110] Minimally, invasive surgery has also been successfully employed in both thoracic and lumbar TVO, including five cases of multi-level infection, and involving differing techniques depending on the level.[111]

Local antibiotic usage

Local antibiotic usage is relatively commonplace in treating prosthetic joint infections but is rarely used in PVO. Vancomycin-loaded cancellous bone grafts within a vertebral body replacement system, or for smaller defects a femoral head inserted in a press fit technique, have been successfully used in eight PVO cases as an adjunct to systemic antimicrobial therapy with the benefit of no systemic toxicity.[112] Additionally, a trial of pellets loaded with gentamicin or vancomycin in 12 PVO patients followed up for 1 year, in addition to systemic antibiotics in all but 1 case, was successful in curing the infection, and revision surgery was required only for instrumentation failure.[113]

Outcomes

There is a wide range of published mortality rates for PVO, 4–29%[3,7,9,11,31,37–40,114–116] across a heterogeneous collection of studies. Since the incidence of VO increases with age, there is a greater likelihood of co-morbidities to influence and interact with the infection and its management. The data from studies on the effect of co-morbidities are not entirely consistent: poor outcomes not associated with co-morbidities,[35] compared with the only significant risk factor for treatment failure on multiple logistic regression being co-morbidities, OR 22.7,[93] mortality significantly associated with co-morbidities and increasing age[3] or Charlson co-morbidities index ≥2 and age ≥60 years,[7] but overall seems to favour a negative effect. In particular, HIV infection (of note, mean CD4 count of patients was 234/μl),[101] haemodialysis (OR 10.56), infective endocarditis (OR 3.19), malignancy (OR 2.68), cirrhosis (OR 2.63) and diabetes mellitus (OR 2.37)[3] have been significantly associated with higher mortality rates, and chronic liver failure significantly increased the risk of neurological complications.[9]

The mortality rate from a retrospective review of 62 patients with spontaneous VO was 29% for osteomyelitis alone but rose to 41% with concomitant endocarditis.[114] Additionally, the co-infected patients were at significantly higher risk of adverse neurological events (59 versus 22%, $P = 0.006$) and 15/17 co-infected patients had highly mobile vegetations on transoesophageal echocardiography with 9 measuring ≥10 mm.[114] A concurrent distant non-spinal site of infection, indicating septic emboli or persistent bacteraemia, was identified as a significant risk factor for neurological complications.[9] Epidural abscess is well recognized as a risk factor for worse outcomes as a result of neurological compromise.[9,35,42] Mortality is significantly higher in cervical VO than at other levels (21.1 versus 3.6%, $P = 0.02$),[9] which may be influenced by the higher incidence of epidural abscesses in the cervical region.[42,62] Paravertebral abscess has also been reported as a risk factor for sequelae.[31]

The premise that isolating the causative organism will favour a more successful outcome has been challenged by four studies: no significant difference in mortality 13.3 versus 8% with and without organism isolation, respectively, among 40 patients with PVO;[116] and no significant effect on treatment outcome.[6,35,93] Mortality was not significantly different between MRSA and MSSA VO, although MRSA was associated with a higher recurrence rate[82,117] and persistent bacteraemia.[82] Mortality, relapse and sequelae rates were not

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significantly different between MSSA and GNB haematogenous VO.[31] Although another study describes *S. aureus* conferring a significantly higher infectious complications rate compared with other organisms (76.5 versus 40.3%, $P = 0.002$), and a non-significant trend to higher mortality was noted.[7] In the RCT, *S. aureus* was significantly associated with treatment failure (69 versus 39%, $P = 0.0012$).[84] However, VO due to *P. acnes* has an excellent prognosis with cure rate 98%.[28] Studies quoting mortality for TVO stated 12.5%[118] and 10.5% but unrelated[30] although co-morbidity was a much greater issue with only 14.7% making a complete recovery and 55.9% partial recovery.[30] The mortality from *Aspergillus* VO is 23%, although only 6/19 deaths were *Aspergillus* related, and a complete response seen in 54%, which is encouraging given overall 47% patients had spinal cord compression.[21]

A study comparing empirical anti-staphylococcal antibiotics versus targeted therapy showed a slower recovery with empirical antibiotics and that these needed changing before the infection would resolve.[119] A delay in diagnosis ≥60 days was significantly associated with poor outcome (relative risk 2.65, $P < 0.05$)[35] and is likely to reflect a delay in effective treatment. A study assessing treatment failure in patients undergoing spinal instrumentation found no significant association with <6 weeks parenteral antibiotic therapy,[102] but the overall treatment failure rate was 23%. The RCT did not show any significant difference in mortality or treatment failure between 6 and 12 weeks treatment.[84] Lastly, CRP >100 mg/l on admission was significantly related to mortality.[7]

Conclusion

VO is an uncommon but important infection with an increasing incidence. Diagnosis remains challenging and can require a high index of suspicion. Further studies are needed to define the most effective technique for spinal biopsies to maximize determining aetiology. The only RCT to date supports shorter (6 weeks) antibiotic treatment, and further high-quality trials are required to provide an evidence base for both the medical and surgical management of VO. The increasing variety of surgical options in terms of approach, technique, staged surgery and types of instrumentation available has led to improved outcomes for patients of various VO presentations by tailoring surgery specific to their needs. Interestingly, there are studies challenging medical management as the first-line choice, and this needs exploring further.

Conflict of interest statement

The authors have no potential conflicts of interest.

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