Spondylodiscitis: update on diagnosis and management

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Spondylodiscitis, a term encompassing vertebral osteomyelitis, spondylitis and discitis, is the main manifestation of haematogenous osteomyelitis in patients aged over 50 years. *Staphylococcus aureus* is the predominant pathogen, accounting for about half of non-tuberculous cases. Diagnosis is difficult and often delayed or missed due to the rarity of the disease and the high frequency of low back pain in the general population. In this review of the published literature, we found no randomized trials on treatment and studies were too heterogeneous to allow comparison. Improvements in surgical and radiological techniques and the discovery of antimicrobial therapy have transformed the outlook for patients with this condition, but morbidity remains significant. Randomized trials are needed to assess optimal treatment duration, route of administration, and the role of combination therapy and newer agents.

Keywords: vertebral osteomyelitis, discitis, spinal infections

Historical perspective

Infection of the spine is an ancient disease, with changes consistent with tuberculosis described in human skeletons dating back to the Iron Age. The first account of pyogenic vertebral osteomyelitis is credited to the French physician Lannelongue in 1879. The first large series of pyogenic vertebral infections in the English literature was published by Kulowski in 1936. Improvements in surgical and radiological techniques and the discovery of antimicrobial therapy have transformed the outlook for patients with this condition, but morbidity remains significant.

Definitions

Spinal infections can be described aetiologically as pyogenic, granulomatous (tuberculous, brucellar, fungal) and parasitic. Pyogenic spinal infections include: spondylodiscitis, a term encompassing vertebral osteomyelitis, spondylitis and discitis, which are considered different manifestations of the same pathological process; epidural abscess, which can be primary or secondary to spondylodiscitis; and facet joint arthropathy. Other anatomical classification schemes exist.

Search methodology

We searched PubMed using the terms (vertebral* OR spinal*) AND (infection* OR osteomyelitis* OR discitis* OR spondylodiscitis* OR septic discitis*) for studies published in English or French between 1 January 1980 and 31 October 2009 and screened the bibliographies of the retrieved articles. In this review, we concentrated mainly on published series of pyogenic spondylodiscitis that involved more than 10 patients; only a few studies were multicentre, or prospective or systematic reviews. No randomized trials for the treatment of pyogenic vertebral osteomyelitis were found, although randomized studies for the prevention of post-operative spinal infections exist. Most studies identified were heterogeneous in design with variable inclusion criteria based on age, aetiology, patient groups and use of a particular diagnostic or treatment modality; direct comparison between studies was therefore not possible.

Epidemiology of spondylodiscitis

Although rare, spondylodiscitis is the main manifestation of haematogenous osteomyelitis in patients aged over 50 years and represents 3–5% of all cases of osteomyelitis. Estimates of its incidence in developed countries range from 4 to 24 per million per year depending on location, era and inclusion criteria of the studies (for example children, tuberculous cases). A number of studies report a bimodal age distribution with peaks at age less than 20 years and in the group aged 50–70 years, though all ages can be affected. Vertebral osteomyelitis has a male preponderance, with a male to female ratio of 1.5–2:1.

The incidence of vertebral infections has been rising through the combined effect of an increase in the susceptible population and improved ascertainment, due to better diagnosis. Two Danish studies from the same group have observed an increase in the prevalence of vertebral osteomyelitis in patients with *Staphylococcus aureus* bacteraemia, doubling from 1.1% to 2.2% in the period from 1980 to 1990. Other reports attribute the increase in spondylodiscitis cases to intravenous drug use, to the rise in healthcare-associated infection, spinal surgery and the increase in the immunosuppressed and ageing population.

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Pathogenesis of pyogenic spondylodiscitis

Pathogens can infect the spine via three routes: by haematogenous spread, by direct external inoculation, or by spread from contiguous tissues. The haematogenous arterial route is predominant, allowing seeding of infection from distant sites onto the vertebral column.

An understanding of the vascular supply of the spine and its development with age is important in distinguishing the two main patterns of disease encountered in adults and children. In children, intraosseous arteries display extensive anastomoses and vascular channels penetrate the disc. Therefore, a septic embolus is unlikely to produce a substantial osseous infarct and the infection is often limited to the disc. By contrast, in adults the disc is avascular and the intraosseous anastomoses involute by the third decade of life, effectively creating end arteries, meaning that a septic embolus results in a large infarct. The subsequent spread of infection to the neighbouring disc and vertebra creates the characteristic lesion of spondylodiscitis. Extensive infarction leads to wedging, cavitation and compression fractures with resulting spinal instability, deformity and risk of cord compression. Uncontrolled infection can breach the bone and track into surrounding soft tissues, causing paravertebral or psoas abscesses, and spread posteriorly into the spinal canal, forming an epidural abscess with further risk of paraplegia, subdural abscess and meningitis.

Of note, pyogenic osteomyelitis of the posterior elements of the vertebrae (pedicles, transverse processes, laminae and posterior spinous processes) is very rarely encountered in haematogenous infections due to their relatively poor blood supply compared with the vertebral body. Posterior involvement is more common with tuberculous and fungal spondylitis, possibly reflecting the relative proportions of blood flow. Cervical lesions are commoner in intravenous drug users. Multifocal involvement occurs in 4% of cases. Tuberculous lesions more commonly affect the thoracic spine in young adults and may be more likely to involve more than two (sometimes non-contiguous) vertebrae compared with pyogenic cases.

Direct inoculation is most commonly iatrogenic following spinal surgery, lumbar puncture or epidural procedures and accounts for up to 25–30% of cases in some spondylodiscitis series. In vertebral infections, the posterior parts are usually affected. Infection of implanted prosthetic material is an important predisposing factor following surgery. Rarely, spondylodiscitis may follow stab or gunshot wounds to the spine.

Contiguous spread is rare. It can occur from any adjacent infective focus, commonly from aortic graft infections, a ruptured oesophagus or a retropharyngeal abscess.

Aetiology and microbiology

A distant focus of infection has been identified in almost half of cases of spondylodiscitis. Mylonas et al. described these to include the genitourinary tract (17%), skin and soft tissue (11%), intravascular devices (5%), gastrointestinal tract (5%), respiratory tract (2%) and the oral cavity (2%). Infective endocarditis was reported in 12%.

Multiple studies report on other predisposing factors. Diabetes mellitus is the most commonly identified risk factor, but others include advanced age, injecting drug use, immunosuppression, malignancy, renal failure, rheumatological disease, liver cirrhosis and previous spinal surgery.

Although a wide range of organisms have been associated with spondylodiscitis (bacterial, mycobacterial, fungal and parasitic), it remains primarily a monomicrobial bacterial infection. S. aureus is the predominant pathogen, accounting for half of non-tuberculous cases (range 20–84%). The proportion of S. aureus bloodstream infections complicated by vertebral osteomyelitis ranges from 1.7% (146 of 8739 cases) to 3% (22 of 724 cases) in two large series. Patients with the highest risk (6% of S. aureus bloodstream infections) are aged over 50 years with community acquisition and no obvious portal of entry of infection. Other risk factors include intravascular device-related bacteraemia in a study by Fowler et al. was 2.2% (7 of 324 cases). Methicillin resistance has increasingly been reported over the last two decades. Whilst the emergence of community-acquired methicillin-resistant S. aureus (MRSA) positive for Panton-Valentine leukocidin causing childhood osteomyelitis is a concern, cases affecting the spine are extremely rare at present. Enterobacteriaceae account for 7%–33% of pyogenic spondylodiscitis cases. Most cases are accounted for by Escherichia coli, the other major members of this group are Proteus, Klebsiella and Enterobacter spp. They are associated with urinary tract infections and older age. In one study of 72 patients, E. coli was isolated exclusively from patients aged over 63 years. Salmonella infection is rare and classically reported in patients with sickle cell disease, although it is also recognized in non-sickle cell disease patients, related to aortic mycotic aneurysms.

Pseudomonas aeruginosa is an uncommon cause of spondylodiscitis. In a series of 61 patients from 1969–79 with a predominantly intravenous drug user population, P. aeruginosa topped the list of pathogens and was isolated in 48% of cases. This finding has not been replicated elsewhere and S. aureus remains the main causative organism in intravenous drug users.

Coagulase-negative staphylococci (CoNS) feature prominently in most large series and account for 5%–16% of cases. Staphylococcus epidermidis is the most frequently identified species and is associated with intracardiac device-related bacteraemia and post-operative infections. There are a few reports of Staphylococcus lugdunensis in the series reviewed. The criteria for determining the significance of CoNS vary, some authors employing parameters such as multiple cultures with the same organism or concurrent infective endocarditis and others interpreting the isolates in the light of the clinical picture and reported resolution of symptoms with targeted treatment.

Streptococci (viridans type and β-haemolytic streptococci, particularly groups A and B) and enterococci are well described causes of spondylodiscitis (5%–20%) and in one study were strongly associated with infective endocarditis (26%) when compared with staphylococcal cases (3%).
Spondylodiscitis: update on diagnosis and management

Streptococcus pneumoniae is a very rare cause of spondylodiscitis. In a large review of 2064 cases of invasive pneumococcal disease, vertebral osteomyelitis was reported in only two cases. Anaerobes constitute rare causes of spondylodiscitis and were observed in less than 4% of cases. Propionibacterium acnes ranks amongst the commonest and is linked with indolent post-operative discitis, often related to implanted material. Bacteroides fragilis and other anaerobes are most commonly associated with contiguous spread from pelvic or intra-abdominal foci of infection. Polymicrobial infections are uncommon and are most likely to result from contiguous spread. They are reported in <10% of cases. However, in one study where all patients underwent biopsy, 51% yielded one organism, 16% two organisms and 8% more than two organisms, suggesting under-recognition in most series.

Brucellosis, the commonest zoonosis in endemic areas, can account for 21–48% of spinal infections, representing the predominant cause in some series from the Mediterranean Basin and the Middle East. Infection occurs secondary to consumption of unpasteurized contaminated dairy products or contact with infected animals. Osteoarticular infections are frequent and a possible genetic susceptibility attributed to allele HLA-B*39 has been described. Spondylitis accounts for 7.5%–30% of cases of brucellosis and is most commonly caused by Brucella melitensis. Patients with brucellosis who develop spondylitis tend to be older and have a longer duration of symptoms.

Tuberculosis (TB) is the commonest cause of spinal infection worldwide, and accounts for 9%–46% of cases in developed countries. Skeletal involvement occurs in 1%–3% of TB infections, half of these affecting the spine. In countries of low TB incidence, it is commonly encountered in ethnic groups originating from areas of high endemicity. In the largest epidemiological study of spondylodiscitis to date, spinal TB was significantly commoner in patients aged under 40 years compared with those over 40 (relative risk 2.7, 95% confidence interval 2.39–3.08). This has also been observed in other series. Patients with brucellosis who develop spondylitis tend to be older and have a longer duration of symptoms.

Diagnosis

Diagnosis is based on clinical, laboratory and radiological features and can be difficult. It is often delayed or missed due to the rarity of the disease, the insidious onset of symptoms and the high frequency of low back pain in the general population. For instance, amongst 109 community-acquired S. aureus bacteraemia cases with vertebral osteomyelitis, the correct diagnosis was only formulated in 5% on admission to hospital, with any vertebral pathology entertained in 39% of the cases.

Clinical features

The symptoms of spondylodiscitis are non-specific. Back or neck pain is very common, but up to 15% of patients may be pain-free. The onset is usually insidious and ‘red flag’ features include constant pain that becomes worse at night. Radicular pain radiating to the chest or abdomen is not uncommon and may lead to misdiagnosis or even unnecessary surgery.

Fever is less commonly experienced and occurs in only about half of patients, and in one series only 14% of 59 cases. Fever is less common in patients with TB spondylitis. Neurological deficits, including leg weakness, paralysis, sensory deficit, radiculopathy and sphincter loss, are present in a third of cases. These are more likely to be associated with epidural abscess, delayed diagnosis, and cerebrospinal fluid, cervical lesions and TB. Risk factors for paralysis also include diabetes mellitus, advanced age and steroid use.

Spinal deformities, predominantly kyphosis and gibbus formation, are commoner in tuberculous spondylitis. Untreated chronic infections can progress to sinus formation, a rare occurrence in recent case series. Cervical spondylodiscitis may manifest with dysphagia or torticollis. Spinal tenderness is the commonest sign detected on examination, reported in 78–97% of cases, often associated with restricted range of movement and paravertebral muscle spasm. A fluctuant mass may be present rarely and sciatic pain can often be elicited.

In children, symptoms of spondylodiscitis are non-specific and include irritability, limping, refusal to crawl, sit or walk, hip pain or even abdominal pain.

Other rarer causes include Actinomyces, Nocardia and cat-scratch disease (in children).

Fungal spondylodiscitis is uncommon even in large series (0.5%–1.6% usually, up to 6.9% in one report). Candida spp., Aspergillus spp. and Cryptococcus neoformans occur worldwide, whilst the dimorphic fungi Coccidioides immitis and Blastomyces dermatitidis are endemic in certain geographic areas. Candida albicans is the commonest reported Candida species in the literature. Risk factors for candidaemia are present in the majority of patients, particularly prior use of broad-spectrum antibiotics and central venous access devices. Other secondary sites of infection are also commonly found (for example, endophthalmitis in 18%).

Parasitic infection, such as Echinococcus infection of the spine, has been reported as a cause and is extremely rare even in endemic areas.

Laboratory features

Haematological and biochemical markers

Erythrocyte sedimentation rate (ESR) is a sensitive marker for infection but lacks specificity. In most reports, it is elevated in over 90% of cases, with mean values ranging from 43 mm/h to 87 mm/h. No relation is found to the severity of the infection or patient age. Carragee and co-workers investigated the ESR trend in predicting response after 1 month of conservative treatment. They found that a fall in ESR to below 25% of the presenting value was a good
prognostic marker: only 3/26 (12%) of cases were deemed clinical failures compared with 9/18 (50%) of those with no significant change in ESR. Thus, an unchanged or rising ESR was more difficult to interpret and the authors suggested evaluating this marker in conjunction with other parameters.

C-reactive protein (CRP) is similarly raised in the large majority of cases with spondylodiscitis. In a study of 29 successfully treated patients, CRP had returned to normal in all survivors at 3 months follow-up. Some authors suggest that CRP is the preferred marker for monitoring response to treatment.

The leucocyte count is the least useful amongst the inflammatory markers; it is high in only a third to half of affected patients. Age did not appear to affect leucocyte count in the study by Belzunegui et al. Other authors have noted an increase in neutrophil count in pyogenic when compared with tuberculous or brucellar spondylitis.

Approximately 70% of patients with spondylodiscitis may be anaemic and about half have a raised alkaline phosphatase serum value.

Microbiological investigations

The value of obtaining a microbiological diagnosis cannot be overemphasized. The wide range of potential pathogens and the rise in antimicrobial resistance, both in hospital and the community, argues for the determination of the causative agent. Empirical broad-spectrum antibiotic therapy is linked to increased rates of complications such as Clostridium difficile-associated diarrhoea and higher healthcare costs and should be reserved for patients presenting with severe sepsis once blood cultures have been taken.

Blood cultures

Blood culture is a simple and cost-effective method for identifying bacterial agents of spondylodiscitis, as the infection is mostly monomicrobial and often has a haematogenous source. The yield from blood cultures varies between 40% and 60% in clinically defined cases of pyogenic spondylodiscitis. The yield is lower in post-operative infections, where biopsy may be needed to confirm the diagnosis, and higher with more virulent organisms and in the presence of pyrexia. Discordant results between blood cultures and biopsy have been reported in one study, including polymicrobial results being missed by blood cultures. In the presence of multiple positive blood cultures with Gram-positive organisms, concurrent infective endocarditis should be excluded.

The use of the Ruiz-Castañeda biphasic blood culture system for the identification of Brucella has now been superseded by automated systems. However, extended incubation for 4 weeks with regular subcultures is recommended.

Biopsy and culture

The frequency of performing biopsies (either open or percutaneous) varied among spondylodiscitis studies, ranging from 19 to 100%, and was often reserved for patients with negative blood cultures. Biopsy cultures from these series (some of which include tuberculous cases) were positive in 43%–78% of cases. The yield from blood cultures varies between 40% and 60% in clinically defined cases of pyogenic spondylodiscitis, a frequency that improved to 79% on repeat biopsy. Other investigators would consider a negative percutaneous biopsy result as an indication for surgical biopsy, especially if the clinical progress is unsatisfactory. Culture positivity is higher with surgical sampling, even when minimally invasive techniques are used; the diagnostic yield can be further improved by submitting more than one specimen for culture.

The value of a percutaneous biopsy as a safe and minimally invasive intervention is well established. Some experts recommend a second percutaneous biopsy if the first one is negative. French guidelines recommend sending six biopsy samples. Biopsy yield is reduced by prior antibiotic use, although as many as 39% of biopsy cultures in suspected cases of spondylodiscitis with no prior antibiotic exposure may be negative.

The role of biopsy in children with spondylodiscitis is debated. Some investigators used it for the majority of their patients, whilst others reserved it for cases that had not responded to empirical therapy or where mycobacterial or fungal agents were suspected.

Biopsy material should undergo aerobic, anaerobic, fungal and mycobacterial cultures. Inoculation into enrichment broth should be considered for fastidious organisms; inoculation of biopsy material into blood culture bottles has been performed by some investigators, but no comparative data exist to support this practice. Biopsy of other sites such as bone marrow may be helpful in brucellosis.

Histology

Histology is a valuable adjunct to culture and can distinguish between pyogenic and granulomatous disease. Special stains, such as Ziehl–Neelsen for mycobacteria and periodic acid–Schiff for fungi, can be helpful. Unsuspected malignancy in proven or presumed cases of spondylodiscitis and vice versa is not uncommon, either due to diagnostic uncertainty or to the susceptibility of this group of patients to infection. This further emphasizes the need for both histological and microbiological analysis of biopsy samples.

Molecular diagnosis

Molecular diagnostic methods using broad-range 16S rDNA PCR have narrowed the diagnostic gap that existed with traditional culture-based methods, especially in the context of prior antibiotic usage or the presence of fastidious microorganisms. Comparisons of spinal biopsy cultures and 16S rDNA PCR have shown high concordance, with improved sensitivity conferred by the latter. 16S rDNA PCR is inferior to culture at detecting mixed organisms due to preferential primer usage or the presence of fastidious microorganisms.
binding. The specificity of 16S rDNA PCR is high in carefully validated methodologies; however, care should be used in interpreting all results when deciding on antibiotic treatment. This is clearly a rapidly evolving field; at present, the role of these methods should be mainly considered as a valuable adjunct to standard cultures.

Serology

Serology should be performed for suspected cases of Brucella or Bartonella henselae infection (particularly in children with cat exposure). Staphylococcal serology has been used, particularly in older case series, and has a reported sensitivity of 80% when anti-alpha- and anti-gamma-haemolysin tests are combined. Nevertheless, its value has been questioned. Antigen-based tests such as the cryptococcal antigen test should be considered when invasive fungal infection is likely.

Radiology

Plain radiography has a reported sensitivity of 82%, specificity of 57% and accuracy of 73%. It is frequently employed as a screening test and may reveal early changes such as subchondral radiolucency, loss of definition of the endplate and loss of disc height. Later changes include destruction of the opposite endplate, loss of vertebral height and paravertebral soft tissue mass. However, changes tend to appear 2–8 weeks after onset of symptoms and false positive results can occur due to degenerative change.

A variety of tracers have been used in the radionuclide imaging of spondylodiscitis. Technetium-99m-methylene diphosphonate bone scintigraphy has a reported sensitivity of 90%, but a poorer specificity of 78%, degenerative changes resulting in false positive results. Gallium-67 scintigraphy is a valuable adjunct to bone scan and when combined they have a sensitivity of 90%, a specificity of 100% and accuracy of 94%. The use of indium-111-leucocyte scan is not recommended due to poor sensitivity, spondylodiscitis lesions often displaying non-specific photopenic regions.

Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is showing promise as a very sensitive modality. It can effectively distinguish infection from degenerative changes even when magnetic resonance imaging (MRI) is inconclusive, although it shows a low specificity for neoplasms.

Computed tomography (CT) is the best modality at delineating bony abnormalities, including early endplate destruction (before they become visible on X-ray), later sequestra or involucra formation, or pathological calcification suggestive of TB. It is inferior to MRI in imaging neural tissue and abscesses. Disc changes appear as hypodense areas. CT is currently mostly used for the radiological guidance of spinal biopsy.

MRI is considered the modality of choice for the radiological diagnosis of spondylodiscitis. It has a reported sensitivity of 96%, specificity of 93% and accuracy of 94%. Its advantage over other modalities lies with its superior ability to provide anatomical information, particularly relating to the epidural space and spinal cord. The characteristic changes consist of decreased signal intensity from disc and adjacent vertebral bodies on T1-weighted images, increased signal intensity on T2-weighted images (due to oedema) and loss of endplate definition on T1 weighting. Gadolinium enhancement of discs, vertebrae and surrounding soft tissues improves the accuracy of MRI, particularly in early infections when other changes may be subtle, and also helps to differentiate infective lesions from degenerative changes (Modic type 1 abnormalities) or neoplasms. TB spinal infection is suggested by a lack of disc involvement (which may cause confusion with neoplasms) and the presence of large paraspinal abscesses, posterior vertebral changes, meningeal enhancement and involvement of multiple non-contiguous levels with greater vertebral bone destruction.

In pyogenic spondylodiscitis, emerging evidence suggests that some MRI changes commonly persist or even worsen during treatment despite clinical improvement and may result in unnecessary surgery. Reliable markers of resolution of infection, such as bony restoration and complete loss of gadolinium enhancement, appear very late in the healing process. Re-imaging in the critical period of 4–8 weeks of treatment showed increased loss of disc height, and often persistent or worsening vertebral body and disc enhancement. MRI signs that often showed improvement include the presence of epidural enhancement, epidural abscess or spinal canal encroachment, but none was associated with the patients’ clinical status. Amongst 21 patients with improved soft tissue MRI features, only one experienced treatment failure whilst most patients with worse appearances did not.

Similar to pyogenic cases, MRI changes lag behind clinical improvement in tuberculous spondylodiscitis and abnormalities can persist past successful completion of treatment. A summary of the non-specific factors that may help in the differentiation of pyogenic, brucellar and tuberculous spinal infections is shown in Table 1.

Treatment

Medical management

The aim of treatment is to eradicate the infection, restore and preserve the structure and function of the spine, and alleviate pain. Conservative management consists of antimicrobial therapy and non-pharmacological treatments such as physiotherapy and immobilization. Immobilization is advocated when pain is significant or there is a risk of spinal instability. Since the advent of antibiotics, mortality has dropped from 25%–56% to less than 5%. However, randomized trials to guide the selection of the appropriate route, duration or agent for antibiotic therapy are lacking. Practice is based on retrospective case series, expert opinion and data extrapolated from animal and laboratory data.

Treatment initiation, route of administration and duration

Whilst initial antimicrobial therapy is almost always administered parenterally, its duration varies considerably. In a multicentre observational prospective study, the mean treatment duration was 14.7 weeks with minimum length ranging from 6 to 12 weeks according to treating centre. Positive blood cultures, neurological abnormalities and staphylococcal infections...
## Table 1. Comparative features between pyogenic, tuberculous and brucellar vertebral infections that may help differentiation (histological and microbiological features not included).

<table>
<thead>
<tr>
<th>Diagnostic parameters</th>
<th>Pyogenic</th>
<th>Tuberculous</th>
<th>Brucellar</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>recent distant bacterial infection</td>
<td>history of TB infection or current extraspinal manifestations</td>
<td>history of Brucella infection</td>
</tr>
<tr>
<td></td>
<td>recent GU surgery or iv access devices</td>
<td>originating from countries with high TB incidence</td>
<td>travel to endemic country, rural areas, consumption of unpasteurized products, occupational history</td>
</tr>
<tr>
<td></td>
<td>previous spinal surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DM, IVDU, chronic debilitation, immunosuppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset</td>
<td>acute or subacute</td>
<td>subacute</td>
<td>acute or subacute</td>
</tr>
<tr>
<td>Clinical findings</td>
<td>pyrexia more common</td>
<td>gibbus deformity more common</td>
<td>gibbus deformity rare</td>
</tr>
<tr>
<td></td>
<td>acute sepsis</td>
<td>pyrexia less common</td>
<td></td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>CRP, ESR, WCC higher, particularly in acutely septic patients</td>
<td>WCC less helpful</td>
<td>WCC less helpful</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CRP, ESR less elevated</td>
</tr>
<tr>
<td></td>
<td>usually lumbar spine</td>
<td>CRP, ESR less elevated</td>
<td>usually lumbar spine</td>
</tr>
<tr>
<td></td>
<td>disc with neighbouring vertebrae affected anterior part of vertebra (except post surgery)</td>
<td>usually thoracic and/or lumbar spine multiple segments</td>
<td>‘parrot beak’ osteophytes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>disc may be spared</td>
<td>vertebral collapse and spinal cord compression are rare</td>
</tr>
<tr>
<td></td>
<td></td>
<td>posterior vertebral elements affected</td>
<td>anterior superior end plate affected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>large paraspinal/psoas abscesses</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>calcification</td>
<td></td>
</tr>
</tbody>
</table>

GU, genitourinary; IV, intravenous; DM, diabetes mellitus; IVDU, intravenous drug user; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WCC, white cell count; CT/MRI, computed tomography/magnetic resonance imaging.
(compared with negative microbiology) were associated with longer intravenous courses.5 Other studies showed a median total treatment duration ranging from 6 to 17 weeks,5,23,47,49,52,153,154,119, with parenteral treatment lasting between 3 and 8 weeks.3,5,23,47,52,153

Sapico and Montgomery22 found a significantly increased risk of treatment failure in patients treated for a total of less than 4 weeks compared with those treated for longer (3 of 7 patients versus 1 of 26 patients respectively). In a retrospective study of 120 patients, no difference in the risk of relapse was found amongst patients treated for ≤6 versus >6 weeks.155 However, the patients treated for more than 6 weeks were older and had higher ESR values and blood culture positivity rates. French guidelines recommend a minimum treatment duration of 6–12 weeks.120

Outpatient parenteral antimicrobial therapy (OPAT) is cost-effective156 and has been used successfully in cases of osteomyelitis; however, data specifically for spondylodiscitis are limited.157 Once daily anti-staphylococcal agents such as ceftriaxone, teicoplanin and daptomycin may be particularly suited for outpatient or home administration.

Criteria for discontinuation of antimicrobial treatment include symptom resolution or improvement and the normalization of ESR or CRP.5,47 It has been proposed that a weekly decrease in CRP by 50% represents adequate progress.12 The role of follow-on oral therapy is not established but treatment has been successful with early oral conversion after as little as 10 days of parenteral treatment.17 Oral agents should have high bioavailability and possible options include fluoroquinolones, clindamycin, rifampicin and fusidic acid.158 Early oral conversion should be avoided until endocarditis has been excluded.99

**Antibiotic choice—empirical and targeted therapy**

Empirical therapy should cover S. aureus and Gram-negative organisms, taking into account local susceptibility rates and the likelihood of colonization with resistant organisms.

Most data on antibiotic bone penetration in humans relates to synovial fluid and long bones.119,158 Antibiotic penetration of β-lactams into healthy human and animal vertebral discs is disappointing,159–161 whilst clindamycin, aminoglycosides and glycopeptides penetrate well into discs in animals. The clinical relevance of these observations is unclear in the context of an infection.

Guidelines exist for the treatment of osteomyelitis caused by TB,162,163 brucellosis,164 MRSA,165,166 Candida,167 Aspergillus168 and dimorphic fungi.159,170 In these, distinction between osteomyelitis affecting the vertebrae and other bones is not always attempted.

Table 2 shows some suggested regimens according to causative organism.

**Role of combination antibiotic therapy**

The role of adjunctive agents for the treatment of S. aureus vertebral infections is not clear. Fusidic acid use in combination with β-lactam antibiotics, macrolides or rifampicin has been reported in a few studies, but the small case numbers and non-comparative nature of the data preclude any firm conclusions.171

The largest observational study to report the use of fusidic acid in combination with a penicillinase-stable penicillin found it was associated with significantly lower recurrence rates compared with β-lactam monotherapy (5% versus 20%).26

A systematic review of the adjunctive use of rifampicin concluded that it offered a benefit, especially in the treatment of prosthetic device and bone infections.172 However, the studies excluded173–175 or did not provide information on cases with vertebral osteomyelitis.176,177 In a series of haematogenous S. aureus spondylodiscitis, cured patients were more likely to have received more than 2 weeks of adjunctive rifampicin compared with patients who relapsed (15 of 30 cases versus 0 of 5 cases respectively). However, this trend did not reach statistical significance.178 A subsequent study of pyogenic spondylodiscitis addressed the empirical use of a quinolone (levofloxacin) and rifampicin,179 a combination considered effective in treating prosthetic device osteomyelitis.175,180 This combination was effective in 77% (37 of 48 cases), rising to 96% (26 of 27 cases) in infection due to confirmed levofloxacin-susceptible organisms (including all 19 S. aureus isolates).179 The efficacy was thought to be related, in part, to quinolone therapeutic drug monitoring, a practice also advocated by others.158 Combinations of quinolone and rifampicin should be used with caution in cases lacking a definitive microbiological diagnosis where TB remains in the differential diagnosis, or where quinolone-resistant Gram-positive organisms (for example MRSA) are prevalent.165

The adjunctive use of aminoglycosides is recommended and used in French studies,119,120,155,158 though this is not supported by clinical evidence and may impair renal function.181

**New antimicrobial agents**

The new anti-staphylococcal agents linezolid, daptomycin and tigecycline are not licensed for use in osteomyelitis. Promising data on daptomycin use in bone infections (including multiple cases of spondylodiscitis) were reported in a recent systematic review of uncontrolled case series.182 In a post hoc analysis of an open-label prospective trial of daptomycin versus standard therapy in 246 patients with S. aureus bacteraemia, 9 cases of vertebral osteomyelitis (3.5%) were identified.183 Daptomycin (6 mg/kg daily) was successful in 4 of 6 patients compared with 1 of 3 treated with standard therapy.183 However, the emergence of resistance on treatment is cause for concern (particularly in isolates with reduced susceptibility to glycopeptides).182

Linezolid has good penetration into bone and excellent oral bioavailability, characteristics that are desirable in the treatment of bone infections.184 In a compassionate use programme, 8 of 55 (15%) patients with bone infections had vertebral osteomyelitis. Of these, four were cured, one was considered a treatment failure and three were non-evaluable.185 The major concern about the use of linezolid in the treatment of spondylodiscitis pertains to its potentially serious side effect profile related to extended treatment courses.186

Tigecycline has been used in an experimental model of long-bone osteomyelitis.187 To our knowledge, no clinical case of spondylodiscitis treated with tigecycline has been described in the literature. Clearly, more data from well-designed trials are needed.

**Challenge of increasing resistance**

Although MRSA bacteraemia rates in the UK are continuing to decline, the reduced efficacy of vancomycin therapy for MRSA

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isolates with vancomycin MIC values of 2 mg/L and above is of concern. To ensure therapeutic vancomycin levels are achieved within infected bone, the Infectious Diseases Society of America (IDSA) guidelines recommend maintaining trough vancomycin concentrations of 15–20 mg/L. It is unclear if adding a second anti-staphylococcal agent or employing a newer agent may be beneficial; this merits further investigation. A French study has highlighted the growing concern regarding drug-resistant tuberculous infection, with 9% of isolates being resistant to at least one first-line agent.

**Surgical management**

Indications for surgical intervention include compression of neural elements, spinal instability due to extensive bony destruction, severe kyphosis, or failure of conservative management. Some also advocate surgery in the presence of intractable pain. Most, but not all, authors consider the presence of epidural abscess as an indication for surgery, even in the absence of neurological deficits. Radiologically guided percutaneous drainage offers an effective alternative to surgery in the management of paravertebral and intradiscal abscesses. However, a more conservative approach in neurologically intact patients is increasingly used with success and has been advocated provided a microbiological diagnosis is available. In such cases, close monitoring is imperative given the risk of sudden neurological deterioration.

Spinal cord compression is a surgical emergency. Outcomes are worse if paralysis has been present for over 24–36 h, when a surgical procedure may be futile. However, some investigators have reported improvement in neurological status following decompression even in patients with prolonged paralysis. A variety of surgical approaches exist and selection depends on patient characteristics and local surgical experience. An

<table>
<thead>
<tr>
<th>Organism</th>
<th>Treatment regimen</th>
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<tbody>
<tr>
<td><strong>S. aureus</strong></td>
<td></td>
</tr>
<tr>
<td>Methicillin-susceptible</td>
<td>Flucloxacillin 2 g q6h iv or equivalent anti-staphylococcal penicillin OR</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone 2 g daily iv</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>Vancomycin 15–20 mg/kg q12h−q8h iv aiming for pre-dose levels of 15–20 mg/L OR</td>
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<tr>
<td></td>
<td>Teicoplanin 12 mg/kg daily iv after loading</td>
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<tr>
<td><strong>Enterobacteriaceae</strong></td>
<td></td>
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<tr>
<td></td>
<td>Ciprofloxacin 400 mg q12h iv or 750 mg q12h orally OR</td>
</tr>
<tr>
<td></td>
<td>Ceftriaxone 2 g daily iv OR</td>
</tr>
<tr>
<td></td>
<td>Meropenem 1 g q8h iv</td>
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<tr>
<td><strong>P. aeruginosa</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceftazidime 2 g q8h iv ± aminoglycosides OR</td>
</tr>
<tr>
<td></td>
<td>Meropenem 1 g q8h iv ± aminoglycosides OR</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin 400 mg q12h iv or 750 mg q12h orally (useful as continuation therapy)*</td>
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<tr>
<td></td>
<td>OR combination of two different antibiotic classes</td>
</tr>
<tr>
<td><strong>Streptococci</strong></td>
<td></td>
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<tr>
<td></td>
<td>Benzylpenicillin 2.4 g q6h iv OR</td>
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<tr>
<td></td>
<td>Ceftriaxone 2 g once daily iv</td>
</tr>
<tr>
<td><strong>Enterococci</strong></td>
<td></td>
</tr>
<tr>
<td>E. faecalis</td>
<td>Amoxicillin 2 g q6h iv ± gentamicin 1 mg/kg q12h−q8h iv</td>
</tr>
<tr>
<td>E. faecium</td>
<td>Vancomycin 15 mg/kg q12h iv ± gentamicin 1 mg/kg q12h−q8h iv</td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
<td></td>
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<tr>
<td></td>
<td>Metronidazole 500 mg q8h iv OR</td>
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<tr>
<td></td>
<td>Clindamycin 450 mg q6h orally</td>
</tr>
<tr>
<td><strong>Brucella</strong></td>
<td></td>
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<tr>
<td></td>
<td>Doxycycline 100 mg q12h orally with streptomycin 15 mg/kg daily im for first 2–3 weeks OR</td>
</tr>
<tr>
<td></td>
<td>Doxycycline 100 mg q12h orally and rifampicin 600–900 mg daily orally</td>
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<tr>
<td><strong>Kingella kingae</strong></td>
<td></td>
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<tr>
<td></td>
<td>Ceftriaxone 2 g daily iv</td>
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<tr>
<td><strong>M. tuberculosis</strong></td>
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<tr>
<td></td>
<td>Isoniazid and rifampicin, with pyrazinamide and ethambutol for the first 2 months</td>
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<tr>
<td><strong>Candida spp.</strong></td>
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<tr>
<td></td>
<td>Fluconazole 400 mg (6 mg/kg) daily iv OR</td>
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<tr>
<td></td>
<td>Liposomal amphotericin B 3–5 mg/kg daily iv OR</td>
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<tr>
<td></td>
<td>an echinocandin</td>
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<tr>
<td><strong>Aspergillus</strong></td>
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<tr>
<td></td>
<td>Voriconazole 6 mg/kg q12h iv loading for two doses, followed by 4 mg/kg q12h iv OR</td>
</tr>
<tr>
<td></td>
<td>Liposomal amphotericin B 3–5 mg/kg daily iv</td>
</tr>
</tbody>
</table>

q6h, every 6 h; q8h, every 8h; q12h every 12 h; iv, intravenously; im, intramuscular

All regimens assume lack of allergy or other contraindications to the recommended agents. Dosages given are for adults with normal renal function. The recommendations are based on local practice (except where reference included).

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anterior approach is preferred as it allows improved visualization of the anterior part of the spine most commonly affected. Posterior decompression by laminectomy should be reserved for isolated primary epidural abscesses and is contraindicated in spondylodiscitis because of the risk of spinal instability. Anterior decompression with either an autologous bone graft or a titanium cage to fill the defect caused by debridement has been described. A more recent approach reports the use of recombinant human bone morphogenetic protein.

Minimally invasive techniques are technically demanding but offer good results in early infection. Percutaneous transpedicular discectomy and drainage resulted in immediate relief of pain in 76% cases.

Outcome

The attributable mortality of spondylodiscitis has been reported as less than 5%, ranging from 0 to 11%. Early mortality is related to uncontrolled sepsis. The most feared complication is disability due to residual neurological deficit or severe pain, occurring in as many as a third of cases. Pelapse rates cannot be accurately determined as the duration of follow-up is not adequate in most series. Recrudescence of infection is known to occur even years after the original insult was treated. In a series of 253 patients followed up for a median of 6.5 years, relapse was documented in 14%. Three-quarters occurred within the first year, the timing ranging from less than 1 month to as long as 12 years post treatment. On multivariate analysis, relapse was associated with recurrent bacteraemia, the presence of a chronically draining sinus and paravertebral abscess. Relapse should be considered in any patient with recurrent pain, unexplained fever, bacteraemia, weight loss or rising ESR.

Independent risk factors for adverse outcome, defined as death or disability, included a delay in diagnosis greater than 2 months, paralysis or motor weakness, and hospital acquisition. In one large series, brucellar infections were associated with serious sequelae less frequently than pyogenic and tuberculous cases.

Childhood spondylodiscitis has an excellent prognosis. In the largest reported series, which included 42 patients, 37 had no functional sequelae, three had pain only on sporting activities, and only one patient had long-term neurological sequelae. In the study with the longest follow-up data (minimum 10 years post infection), 80% (16 of 20 patients) were completely asymptomatic, whilst 20% had restricted spinal movement.

Conclusion

Spondylodiscitis remains rare but its incidence is rising, due to an increasingly susceptible population and the availability of more effective diagnostic tools. A high index of suspicion is needed for prompt diagnosis to ensure improved long-term outcomes. A microbiological diagnosis is essential to enable appropriate choice of therapeutic agents. Randomized trials are needed to assess the optimal treatment duration, route of administration, and the role of combination therapy and newer agents.

Surgery has an important role in alleviating pain, correcting deformities and neural compromise and restoring function.

Transparency declaration

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