



# Spondylodiscitis revisited

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- Spondylodiscitis may involve the vertebral bodies, intervertebral discs, paravertebral structures and spinal canal, with potentially high morbidity and mortality rates.
- A rise in the susceptible population and improved diagnosis have increased the reported incidence of the disease in recent years.
- Blood cultures, appropriate imaging and biopsy are essential for diagnosis and treatment.
- Most patients are successfully treated by conservative means; however, some patients may require surgical treatment.
- Surgical indications include doubtful diagnosis, progressive neurological deficits, progressive spinal deformity, failure to respond to treatment, and unresolved pain.

**Keywords:** spondylodiscitis; spondylitis; discitis; spinal infection; vertebral osteomyelitis

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Infections of the spine have a large spectrum of clinical manifestations. The vertebral bodies, intervertebral discs, spinal canal and paravertebral structures may be involved.<sup>1</sup> Spinal infections can be aetiologically classified as pyogenic (bacterial), granulomatous (tuberculous or fungal) and parasitic (*Echinococcosis*).<sup>2</sup> Based on the specific anatomical elements involved, spinal infections may also be classified as spondylitis (vertebral osteomyelitis), discitis, epidural abscess or facet joint arthropathy.<sup>3</sup> Nevertheless, alternative anatomical classifications also exist.<sup>4</sup>

Historically, spinal infection is reported as an ancient clinical condition. There is evidence of such infection in human skeletons dating back to the Iron Age.<sup>5</sup> Spinal surgery was initially developed as an effort to treat vertebral

infection. The first spinal fusion was performed in 1911 by Hibbs, on a patient with spinal tuberculosis (TB) in an attempt to prevent disease progression.<sup>6</sup>

Although the course and the consequences of the disease are well recognised, optimal treatment is still controversial and precise recommendations are few. In recent years, with the advent of systemic antibiotic agents and better understanding of the natural history of the disease, conservative treatment has become the standard of care. However, surgical indications for the treatment of spinal infections still exist.<sup>7</sup> This review discusses the epidemiology, pathogenesis, clinical manifestations, diagnosis and treatment of spondylodiscitis, based on current evidence.

## Epidemiology

Spondylodiscitis represents 0.15% to 5% of all osteomyelitis cases.<sup>8,9</sup> At the same time, it constitutes the main manifestation of haematogenously-spread osteomyelitis in patients over 50 years of age.<sup>10</sup> In the developed world, the estimated incidence of the disease ranges from four to 24 patients per million per year.<sup>11–14</sup> Vertebral osteomyelitis demonstrates a male predominance, with a male-to-female ratio of 1.5 to 2:1.<sup>12,15</sup> In recent decades, the incidence of vertebral infection has risen. This has been attributed to the increase in susceptible population (advanced age, immunocompromised states such as HIV infection, intravenous drug users), healthcare-associated infections, expansion of spinal surgery indications and improved diagnostic modalities.<sup>16</sup>

## Risk factors

A low socioeconomic status has been associated with the presence of spinal infection. People who live in poverty, with inadequate sanitation and limited access to

healthcare often remain undiagnosed until the peak of their symptoms, and sometimes present in a precarious health state.<sup>17</sup> The most common predisposing factors include a previous infection such as of the skin and soft tissues or intravascular implants, or genitourinary, gastrointestinal, respiratory and oral cavity infections,<sup>16</sup> advanced age,<sup>14</sup> intravenous drug use,<sup>18</sup> HIV infection,<sup>19</sup> immunosuppression<sup>20</sup> and underlying co-morbidities such as renal failure, rheumatological disease and hepatic cirrhosis.<sup>21</sup> Urinary tract infections are common (17%) and range from cystitis to pyelonephritis.<sup>16</sup> An underlying malignancy is also reported to be a risk factor for spondylodiscitis, and therefore its potential presence should be investigated.<sup>22</sup> Furthermore, previous spinal surgery and outpatient spinal procedures are considered to be major risk factors (39.2% of cases).<sup>1</sup>

## Pathogens

TB used to represent the most frequent cause of spinal infection. In the late 1950s, a study concluded that TB was the aetiological agent in 59% of cases.<sup>23</sup> In recent decades the responsible agents have changed. A study in 2010 showed that the majority of spinal infections were pyogenic in origin, whilst TB infection was detected in less than a quarter of all cases.<sup>24</sup> In recent years, *Staphylococcus aureus* has become the most frequent bacterium responsible for vertebral infections, accounting for 20% to 84% of all cases.<sup>16,25-27</sup> Additionally, *Enterobacteriae spp.* are implicated in 7% to 33% of pyogenic vertebral infections. *Escherichia coli* is the most common pathogen in this group, followed by *Proteus*, *Klebsiella* and *Enterobacteriae spp.* These isolates are often associated with urinary or gastrointestinal tract infections, advanced age, states of immunosuppression and diabetes.<sup>16,28</sup> In the same group, *Salmonella* spinal infection is reported to be extremely rare, seen mostly in children with sickle-cell disease.<sup>29</sup> Likewise, *Pseudomonas aeruginosa* is responsible for only a few cases and is associated with intravenous drug abuse, even though *Staphylococcus aureus* is still the predominant aetiological agent in drug users.<sup>30,31</sup> *Streptococci* and *Enterococci* are also common causes,<sup>32</sup> being responsible for 5% to 20% of cases, whereas anaerobes are isolated in less than 4%.<sup>16</sup> *Staphylococcus epidermidis* is associated with implant-related infections, whereas coagulase-negative *Staphylococci* and *Streptococcus viridans* may be a cause of indolent infections, due to their low virulence. On the other hand, the common zoonotic bacterium *Brucella* is still endemic in some Mediterranean and Middle Eastern countries. Spinal involvement in brucellosis is seen in 6% to 12% of cases, representing an important cause of spinal infection in these regions.<sup>33</sup> Fungal infections are extremely rare, mostly responsible for opportunistic infections in immunocompromised individuals.

Similarly, *Echinococcal* spine infection is quite rare, mostly described in endemic areas; these are countries of the temperate zones including southern South America, the entire Mediterranean littoral, southern and central parts of the former Soviet Union, central Asia, China, Australia and parts of Africa.<sup>34</sup> In children, the most common isolates in spondylodiscitis are *Staphylococcus aureus* and *Streptococcus spp.*, whereas strains of *Kingella kingae* constitute another very significant cause.<sup>35</sup> In approximately one-third of patients the implicated organism may not be isolated.<sup>36</sup> Despite the wide range of pathogens that have been associated with spondylodiscitis, it is considered to be a mono-microbial rather than a poly-microbial infection, most of the time. The latter concerns < 10% of cases and it is mostly reported after contiguous infection spread.<sup>37</sup>

A distant infection site has been identified in almost half of spondylodiscitis patients.<sup>16,37</sup> Common distant infection sites include the genitourinary tract (17%), the heart (endocarditis, 12%), skin and soft tissue (11%), intravascular devices (5%), gastrointestinal tract (5%), respiratory tract (2%) and oral cavity (2%).

## Pathogenesis

There are two main infection routes that may contribute to the development of spinal infection. Infectious spread may be haematogenous or non-haematogenous, the latter being either the result of direct external bacterial inoculation or extension from a contiguous infectious site. Haematogenous spread is the most common route, allowing bacteria from distant sites to contaminate the spine in the setting of bacteremia. The origin of infection in these patients may be the oral cavity, the skin, the respiratory, urinary or gastrointestinal tract, or any infected implanted device. Wiley and Trueta<sup>38</sup> demonstrated how metaphyseal and cartilaginous end-plates constitute potential areas of inoculation after bacterial spread in the arteriolar network. Infection in pyogenic spondylodiscitis begins when bacteria reach the metaphyseal vascular arcades, whereas the intervertebral disc is destroyed by the release of bacterial proteolytic enzymes, a process similar to cartilage destruction in septic arthritis. On the other hand, TB infection usually begins after venous spread through Batson's venous plexus. In contrast to pyogenic spondylodiscitis, the latter type of infection typically preserves the adjacent vertebral discs until late in the disease process.<sup>39</sup>

The pathophysiology of spinal infection is somewhat different in adults and children. Discitis is common in children, due to the persistent vascularisation of the vertebral disc that may provide a nidus for bacterial inoculation in the setting of bacteremia.<sup>40</sup> Accordingly, the vertebral body is relatively protected in children. The metaphysis in children has a rich blood network with anastomotic arterioles that

protects the body from extensive destruction in case of infarction by septic emboli. In adults, however, intra-osseous arteries are end-arteries and septic emboli may become entrapped, resulting in extensive destruction, leading to wedging or collapse of the body.<sup>41</sup> Infection extending to the adjacent disc and vertebra creates the typical lesions of spondylodiscitis. In contrast to TB and fungal infections, the posterior vertebral structures are rarely involved in haematogenous pyogenic infection.<sup>42</sup> The poor blood supply of these structures explains their limited involvement.<sup>43</sup> Extensive vertebral destruction may result in deformity, compromise stability or cause spinal cord compression. Uncontrolled infection may lead to the formation of paravertebral abscesses or may spread into the spinal canal. Such contamination may result in meningitis, epidural or subdural abscess formation, neurological impairment and high morbidity and mortality rates.<sup>44</sup>

Direct bacterial inoculation is mainly iatrogenic. A diagnostic or therapeutic spinal procedure may inoculate bacteria and contaminate the spine. Iatrogenic inoculation accounts for 14% to 26% of spinal infections.<sup>45</sup> Contiguous spread is extremely rare. Infection in these cases may spread from adjacent infected tissues such as a ruptured oesophagus or an infected aortic graft.<sup>46,47</sup>

## Spinal regions

Hematogenous pyogenic spondylodiscitis affects mostly the lumbar spine followed by the thoracic, cervical and sacral regions.<sup>48</sup> TB commonly affects the thoracolumbar spine;<sup>49-52</sup> TB involvement of the cervical and lumbosacral spine is less common, whereas TB of the cranio-vertebral junction is rare.<sup>53</sup> Patients with pyogenic infection mostly present with isolated lesions, involving one or two adjacent vertebrae. In contrast, most of the patients suffering from TB spondylodiscitis present with more than two infected vertebrae and about 25% of them with multifocal skip lesions.<sup>49</sup>

## Clinical manifestations

Clinical presentation of spondylodiscitis is generally vague and non-specific.<sup>54</sup> The most common symptom is back or neck pain, typically worse at night. During physical examination, in the majority of cases, tenderness, paravertebral muscle spasm and restricted spinal range of movement are observed.<sup>55</sup> High fever is reported in about half of spondylodiscitis cases, being less common in patients with TB.<sup>56</sup> Moreover, TB is usually associated with a more insidious clinical course and a delayed onset of symptoms, as compared with pyogenic infections.<sup>9</sup> Spinal TB typically presents with back pain, tenderness mostly in the thoracolumbar spine and localised back deformity. In

addition, cervical spondylodiscitis may cause dysphagia or torticollis.<sup>57</sup> Other non-specific symptoms include malaise, lethargy, confusion, nausea, vomiting, anorexia and weight loss.<sup>58</sup> Neurological deficits at presentation are not infrequent (27%); these include paralysis, sensory deficits, muscle weakness, radiculopathy and sphincter dysfunction as a result of spinal cord or cauda equina compression.<sup>58</sup> Non-specific cardiac symptoms such as malaise, weakness, excessive sweat and fever may suggest subacute bacterial endocarditis. In this setting, an echocardiogram is an important diagnostic test in patients with haematogenous spinal infections.<sup>16,37</sup>

In children, abdominal pain may be present, especially when the lumbar spine is affected. Other symptoms may include low-grade fever, difficulty in walking, irritability and inability to bend over. Back pain that worsens with movement is commonly the leading complaint. Obtaining a detailed history and physical examination may be problematic in children, due to communication difficulties. As compared with adults, neurological deficit in these patients is uncommon.<sup>59</sup>

In the elderly, the diagnosis of spondylodiscitis is frequently delayed. The reasons for this include a higher prevalence of co-morbidities such as degenerative back pain that may cloud diagnostic thinking. Clinical assessment may be difficult because of pre-existing cognitive impairment or intercurrent delirium and atypical or subtler symptoms and biochemical marker abnormalities. Relatively few spinal infection studies specifically deal with older populations, and data on spinal infections in adults is similarly sparse.<sup>60</sup>

## Laboratory findings

Laboratory tests are usually inconclusive in diagnosing spondylodiscitis. White blood cell count (WBC) is of limited diagnostic value, as it is commonly non-specific, being elevated in less than half of patients.<sup>21</sup> Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are more helpful.<sup>55</sup> ESR is a sensitive laboratory test, being elevated in > 90% of patients, with a typical range of 43 mm to 87 mm per hour.<sup>61</sup> CRP is more sensitive than ESR, with its levels also elevated in most cases.<sup>55</sup> Nevertheless, these markers are also non-specific, since they are unable to distinguish between a pyogenic, granulomatous or other inflammatory process. Obviously, patients with acute disease may demonstrate a significant increase of these markers, while in chronic infections (as in TB infections) these values may be normal or only slightly elevated.<sup>8</sup>

WBC is not very useful for the diagnosis of spinal infection, but should be part of the work-up, as it may provide information concerning response to treatment. CRP levels and ESR are more reliable to evaluate treatment response



**Fig. 1** Lateral radiograph of the thoracolumbar spine of a 70-year-old patient with pyogenic spondylodiscitis that originated from an infected pacemaker shows partial collapse of the T11 and T12 vertebral bodies and T11 to T12 disc degeneration.

or detect the onset of a post-operative infection after a spinal procedure.<sup>21</sup> CRP presents higher clinical value as it normalises faster than ESR after appropriate treatment.<sup>55</sup> An increase or decrease of CRP levels is directly related to deterioration or improvement of the clinical course, respectively.<sup>62</sup> Other findings include anaemia (approximately 70% of patients) and elevated serum levels of alkaline phosphatase (approximately 50% of patients).<sup>16</sup>

If spondylodiscitis is suspected, it is essential to obtain blood and urine cultures before administration of antibiotics. Multiple blood samples are recommended. The pathogen may be detected not only in the febrile or the critically ill, but also in afebrile patients.<sup>63</sup> Blood cultures are reported to be positive in 58% of cases (range, 30% to 78%), and approximately 25% to 59% of positive cultures identify the causative organism.<sup>37,61,64</sup> However, in post-operative infections, blood cultures are often negative.<sup>21</sup>

## Biopsy

In general, when spinal infection is suspected and blood cultures are negative, biopsy should be performed. Biopsy is considered to be a superior diagnostic tool and may also be performed to verify diagnosis in suspicious cases, or when a polymicrobial infection is suspected, regardless of the presence of positive blood culture.<sup>18,65</sup>

Percutaneous CT-guided biopsy is the standard of care for the diagnosis of spondylodiscitis of unidentified

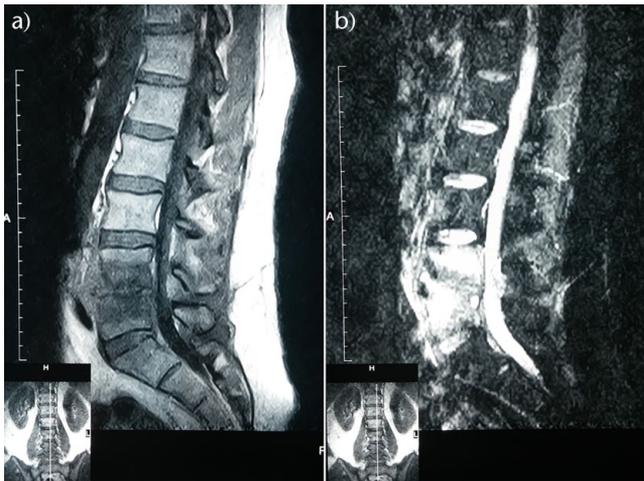
origin.<sup>65</sup> The yield of CT-guided biopsy is reported to be up to 75%.<sup>3</sup> In cases of negative results, some authors advise the conduction of a second percutaneous biopsy, whereas others advise the conduction of an open biopsy.<sup>66,67</sup> CT-guided biopsy can also be performed in children with an accuracy up to 80%. However, open biopsy is argued due to increased local morbidity.<sup>59</sup> Lower yield is expected if patients were treated with antibiotics before blood cultures or biopsy, and false negative results are frequent. In such cases, providing that the patient is stable, biopsy should preferably be performed 48 hours after the most recent antibiotic dose.<sup>68</sup> Nonetheless, some authors reported significant false negative results after CT-guided biopsy in the absence of prior antibiotic administration (39%) and confirmation of the infection with further histological evaluation.<sup>69</sup> For this reason, for optimum diagnosis, fluid and tissue specimens for aerobic, anaerobic, fungal and mycobacterial cultures, as well as histology, should be submitted.<sup>67</sup> Histopathological analysis is able to distinguish between infection and contamination, as well as between pyogenic and granulomatous disease.<sup>42,68</sup> Additionally, it may reveal a potential underlying malignancy.

## Other laboratory tests

Even though they are not able to differentiate between active and latent disease, important information may also be obtained by the tuberculin skin test and interferon-gamma release assays, if a TB infection is suspected,<sup>70</sup> and serological tests may be performed if *Brucella* infection is suspected.<sup>71</sup> Another useful diagnostic method is amplification-based DNA analysis via polymerase chain reaction (PCR). PCR seems to have higher sensitivity as compared with cultures, but it is inferior in cases of polymicrobial infections. Therefore, it is a useful adjunct to cultures, rather than a substitute for them. It may be used to confirm culture results in cases of unusual pathogens, to recognise sample contamination and to identify promptly slow-growing bacteria and contribute to a species-specific therapeutic approach.<sup>72</sup>

## Radiographs

Even though radiographs of the spine have a low specificity for the evaluation of spondylodiscitis (57%), they are regarded as a vital baseline examination.<sup>65</sup> They may provide evidence suggestive of vertebral infection, paravertebral abscess formation or spinal deformity, and may also differentiate between other clinical conditions, such as bone metastases or osteoporotic fractures (Fig. 1). Radiographs may reveal the extent of bone destruction and indicate coronal or sagittal malalignment secondary to disease progression.<sup>61</sup> Radiographs are reported to show



**Fig. 2** Sagittal (a) T1-weighted and (b) T2-weighted MRI of the lumbar spine of a 45-year-old patient with spontaneous pyogenic spondylodiscitis showing reduction of the L4 to L5 vertebral disc height and erosion of the adjacent vertebral end-plates.

abnormalities of the infected spine in almost 90% of cases.<sup>37</sup> However, sensitivity and specificity of radiographs are expected to be lower in early disease stages, as the first radiographic signs may appear two to eight weeks after the onset of infection.<sup>45</sup> In pyogenic spondylodiscitis, narrowing of the disc space represents the earliest finding, followed by blurring and irregularity of the end-plate.<sup>61</sup> This happens due to disc and bone degeneration by the released proteolytic enzymes. In early TB, however, considering the absence of these enzymes, the disc space is generally preserved.<sup>9</sup> Nonetheless, after eight to 12 weeks, significant bone destruction is obvious.<sup>61</sup>

In children, four radiographic phases of discitis have been described; these include the latent, acute, healing and late phase. In the latent phase, plain radiographs are normal, whilst in the acute phase (two to four weeks later) erosion of the disc space is evident. In the healing phase (two to three months later), sclerosis of the contours of the vertebral bodies is evident, and in the late phase, narrowing of the involved disc space is observed.<sup>73</sup>

### Computed tomography

Computed tomography (CT) can further characterise bone lesions, as it is more sensitive than radiographs, due to its higher soft-tissue contrast resolution. In early disease stages, end-plate destruction, reduction of paravertebral fat and disc hypodensity may be evident. During disease progression, erosion of the end-plates and sequestra formation may be seen. Bone necrosis and pathological calcification suggestive of TB infection, as well as paravertebral disease extension or epidural abscess formation, can also

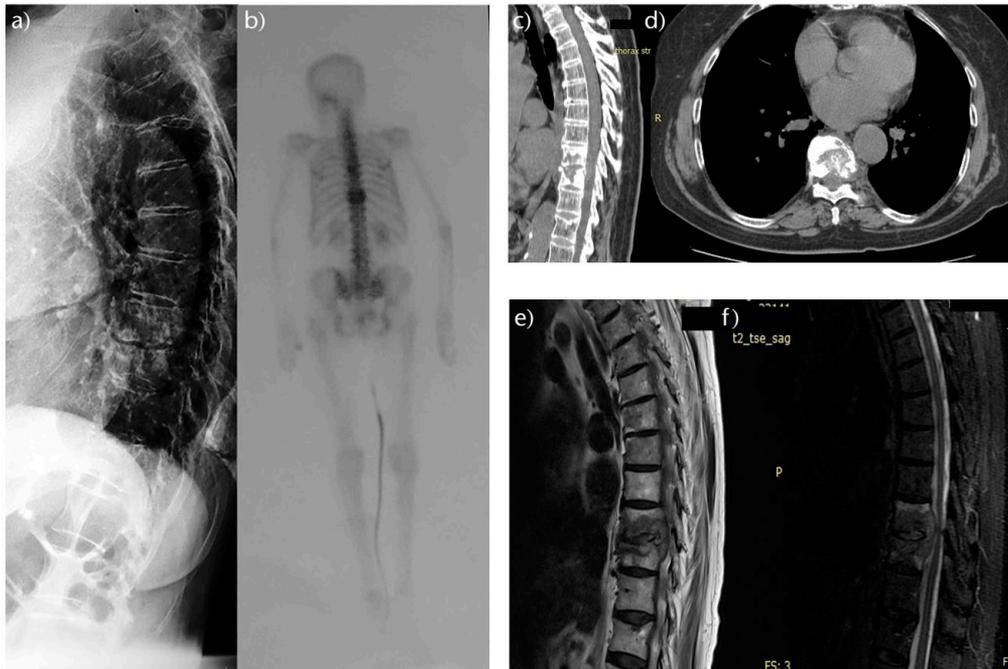
be detected.<sup>74</sup> Even if CT provides a more conclusive evaluation of bone integrity and it is more sensitive to earlier changes than radiographs, it is inferior to magnetic resonance imaging (MRI), being generally reserved for the conduction of CT-guided biopsy or if MRI is contraindicated.

### MRI

MRI is considered the imaging modality of choice for the detection and evaluation of spondylodiscitis, giving 96% sensitivity, 92% specificity and 94% accuracy.<sup>75</sup> In acute spinal infections, an increase in fluid signal due to marrow oedema is demonstrated. The infection mostly begins in the anterolateral vertebral body near the end-plates, presenting irregular signal intensity on T1-weighted images, while the associated oedema typically affects most of the body and adjacent disc.<sup>75</sup> In this setting, typical findings of pyogenic infection include low signal on T1- and high signal on T2-weighted images, with enhancement of the involved vertebral bodies on T1-weighted images after contrast medium administration (Fig. 2). Additionally, high signal on T2 images, loss of intranuclear cleft and peripheral enhancement of the infected disc are shown.<sup>76,77</sup>

Intra-osseous abscesses, large paravertebral abscesses, skip lesions, contiguous subligamentous spread, involvement of the posterior elements and encroachment on the spinal canal and nerve roots are suggestive of TB spondylodiscitis.<sup>77,78</sup> Another MRI feature in patients with TB infection is the relative preservation of the disc, whilst it is also reported that the chronic course of the disease contributes to the formation of thinner and smoother abscess walls.<sup>79</sup> In *Brucella* infection, intact vertebral architecture is observed, despite the evidence of diffuse vertebral infection. An increase in signal intensity of the disc on T2-weighted and contrast-enhanced images, as well as facet joint involvement are also characteristic findings.<sup>80</sup> Paravertebral abscesses tend to be smaller than those in TB infections. However, it can be difficult to differentiate between *Brucella* and TB spinal infections.<sup>81</sup> Most fungal spinal infections present with non-specific findings on MRI, whilst vertebral body destruction in this type of disease may mimic TB infections. Absence of signal increase on T2-weighted images, and low or undetectable enhancement after contrast administration may be MRI features of fungal infection.<sup>76</sup>

As MRI in spinal infections can result in images that mimic malignancy, biopsy may be warranted.<sup>66</sup> Additionally, MRI may overestimate the extent of the infected tissue. Therefore, additional information from radiographs or CT may be necessary for the definition of the real amount of tissue necrosis.<sup>61</sup> Finally, the results of MRI in both pyogenic and TB spondylodiscitis are not always in agreement with the clinical course of the disease. Abnormal findings may persist even after successful treatment. An early sign of healing (from a few weeks to a few months



**Fig. 3** (a) Lateral radiograph of the thoracic spine, (b)  $^{99m}\text{Tc}$ -MDP bone scan, (c) sagittal and (d) axial CT, and sagittal (e) T1-weighted and (f) T2-weighted MRI of the spine of an 83-year-old woman with tuberculosis spondylodiscitis showing increased radionuclide uptake and destruction of the T9 to T10 vertebrae.

after successful treatment) on MRI is the reduction of contrast enhancement. The absence of enhancement and return to normal signal pattern are reliable features of healing after spondylodiscitis. However, some degree of contrast uptake may be present for many months, being more likely to involve the disc rather than the vertebral body.<sup>82</sup> In this context, the interpretation of MRI findings in the follow-up period should be treated with caution.

### Nuclear imaging

In the absence of abnormal radiographic findings or when MRI is inconclusive, radionuclide imaging modalities may aid diagnosis. Three-phase bone scintigraphy with technetium-99m is very sensitive (90%) within a few days of infection onset.<sup>75</sup> However, it gives limited specificity and is inferior in terms of resolution of the relevant anatomical structures (Fig. 3). Gallium-67 (Ga-67) scintigraphy with single-photon-emission CT (SPECT) is more reliable in the evaluation of spinal infections, with a reported accuracy of 67%. This method, though, has comparative results with MRI and for this reason it is mostly reserved for cases in which MRI is inconclusive or contraindicated.<sup>83</sup> The combination of  $^{99m}\text{Tc}$  methylene diphosphonate (MDP) and Ga-67 scintigraphy and conventional CT (SPECT-CT) is reported to offer even higher accuracy.<sup>84</sup> Fluorine-18 fluorodeoxyglucose positron

emission tomography is another promising method, reported to have higher sensitivity, specificity and accuracy in spinal infections.<sup>85</sup> Results are comparable with MRI in patients with high and medium grade spinal infections, whereas it seems to be superior in detecting low grade infections.<sup>86</sup> However, this method is not widely available and evidence regarding its usefulness and cost-effectiveness is still limited.<sup>87</sup>

### Conservative treatment

The goal of treatment for patients with spondylodiscitis is eradication of infection, preservation or restoration of spinal structure, stability and neurological deficits, and relief of pain. Conservative treatment constitutes the standard of care and most patients are successfully treated with non-operative means. In this context, appropriate antibiotics in combination with non-pharmacological regimes, such as immobilisation and physical therapy, are effective in most cases.

Immobilisation with bed rest or with bracing decreases pain, stabilises the spine and prevents deformity. Initially, bed rest is recommended in the first stages of disease, until acute pain resolves, generally lasting no longer than two weeks. Ambulation using a brace is recommended thereafter. If the cervical spine is involved, a collar or a halo-vest may be applied. A reclining brace may be

indicated for thoracic spine lesions. This brace immobilises the affected spine in the reclining position, reducing the load on the infected vertebrae by distributing weight to the unaffected facet joints. Accordingly, a thoracolumbar or lumbosacral brace may be applied, if the thoracolumbar or lumbar spine is affected. In the presence of major defects in the anterior column in the lower lumbar or the lumbosacral spine, bed rest is claimed to be necessary for at least six weeks. Nevertheless, immobilisation-related morbidity, especially in the elderly, should be considered. Bed rest may result in skin ulcerations, deep vein thrombosis, pulmonary embolism or pneumonia. In addition, high rates of pseudarthrosis and instability that may result in spinal deformity and chronic pain have been reported (16% to 50%). Therefore, conservative treatment discontinuation may be advisable after four to six weeks. If there are no radiological signs of bone fusion, destruction progresses or there is no clinical improvement,<sup>8,88</sup> prompt treatment with antibiotics is essential. However, antibiotic administration should be initiated preferably after isolation of the pathogenic organism and consideration of the relevant susceptibility data. This is feasible in most cases, provided that the patient does not receive antibiotic agents before cultures or biopsy. The initiation of treatment may be withheld until a conclusive result, as long as the patient's condition is stable.<sup>89</sup>

A variety of agents may be employed for the management of spinal infections. In cases of methicillin-susceptible *Staphylococci*, an anti-staphylococcal penicillin or a first-generation cephalosporin are the antibiotic agents of choice. For methicillin-resistant organisms, including most of *Staphylococcus epidermidis* cases, a glycopeptide such as vancomycin may be administered. Linezolid and quinupristin-dalfopristin are alternative options. Additionally, in cases of *Streptococcus spp.*, penicillin G is the agent of choice. For gram-negative bacteria, a cephalosporin or a quinolone could be administered, whereas in cases of anaerobes, metronidazole or clindamycin may be used. In TB spondylodiscitis, multiple agents are administered due to potential resistance.<sup>90</sup> The antimicrobial regime classically includes isoniazid, rifampicin, ethambutol and pyrazinamide. In *Brucella* infections, treatment with doxycycline and streptomycin or gentamicin may be needed. Fungal infections may require treatment with an azole or amphotericin B.<sup>89</sup> It should be emphasised, however, that the antibiotic regime has to be tailored to the specific pathogen according to cultures and sensitivities.

The duration of antimicrobial therapy is controversial. There are diverse recommendations for duration of treatment, ranging from four to six weeks to three months, based mostly on observational studies and expert opinions.<sup>68,91</sup> A recent randomised controlled trial including 359 patients showed that six weeks of antibiotic treatment was not inferior to 12 weeks. The authors assigned 176

patients to a six-week and 175 patients to a 12-week antibiotic regime. Almost 91% of patients in the first group and 91% in the second had a clinical cure, with similar rates of adverse events in both groups; death rate was 8% versus 7%, antibiotic intolerance 7% versus 5%, cardiorespiratory failure 4% versus 7% and neurological complications 4% versus 2%. The authors suggested that the standard antibiotic treatment duration for patients with pyogenic spondylodiscitis could be limited to six weeks.<sup>92</sup>

Likewise, the optimal duration of treatment in *Brucella* spondylodiscitis is unknown, but treatment of at least three to six months should be beneficial.<sup>93</sup> In TB spondylodiscitis, antimicrobial agents are generally administered for nine to 12 months, which may be extended to 18 to 24 months to allow complete healing and prevent relapse.<sup>8,89</sup> A full antimicrobial regime is recommended for the first two months, followed by part of the regime according to sensitivities.<sup>89</sup> In these patients, compliance is essential to prevent multi-drug resistance, especially when the patients are immunocompromised.<sup>94</sup> On the other hand, the duration of antifungal treatment needs to be individualised with respect to side-effects and clinical response.<sup>95</sup> Finally, in patients with undrained abscesses or infected spinal instrumentation, prolonged antibiotic treatment is generally recommended.<sup>68</sup>

In general, administration of intravenous antibiotics as initial treatment for at least two to four weeks is recommended to improve bioactivity.<sup>88</sup> Higher treatment failure rates are reported in cases with parenteral administration for less than four weeks.<sup>96</sup> However, switching to an oral regimen after a two-week intravenous treatment is also reported to be effective, if enlarged epidural or paravertebral abscesses have been drained and CRP levels have decreased.<sup>97</sup> Peroral agents with high bioavailability, such as fluoroquinolones, allow for an early switch to oral administration.<sup>68</sup> Clindamycin has good bioavailability and is effective for prolonged treatment of chronic staphylococcal osteomyelitis, but there are limited data for treatment of acute staphylococcal disease in adults. Furthermore, the low bioavailability of beta-lactam antibiotics does not allow for oral administration.<sup>68</sup>

Antibiotics should not be started in children before pathogen isolation, provided that they are not critically ill. However, there are reports that support empirical antibiotic treatment in children, considering the likely probability of the involved pathogen as well as the related risk factors. Considering that the most common isolates are *Staphylococcus aureus* and *Streptococcus*, a combined regime of a third generation cephalosporin and oxacillin/clindamycin is recommended.<sup>59</sup>

As in adults, there are no standardised guidelines for the duration of antibiotic treatment in children. Intravenous administration for one to three weeks followed by oral antibiotic agents until clinical improvement is

generally employed. According to the patient's response, the total duration of treatment may range from two weeks to six months.<sup>59</sup> Conversely, some authors doubt the bacterial origin of spondylodiscitis in childhood, questioning the need of antimicrobial regimes, as self-limiting disc inflammation that resolved without antibiotics has been observed.<sup>40</sup> Regardless of a patient's age, the criteria for antimicrobial treatment discontinuation are clinical improvement, resolution of symptoms and normalisation of ESR and CRP values. A weekly decrease of CRP levels by 50% has been proposed as an adequate progress index.<sup>16,59</sup> In contrast, lack of clinical improvement over a four-week period, continued fever, pain and persistently high CRP levels (above 30 mg/l) are predictors of treatment failure.<sup>68</sup>

## Surgical treatment

Conservative treatment is the standard of care for patients with spondylodiscitis, using multidisciplinary approaches involving microbiologists, infectious disease consultants, anaesthetists, intensivists and geriatricians, with public health physicians for contact tracing. The morbidity and mortality of patients with spondylodiscitis treated conservatively has fallen from 56% to 25% over the last 15 years.<sup>7,9</sup> However, careful selection of patients who need surgical treatment is necessary.

Surgical treatment is absolutely indicated in patients with spinal cord or cauda equina compression with progressive neurological deficits. Relative surgical indications include spinal instability due to extensive bone destruction, significant deformity or conservative treatment failure.<sup>61,98,99</sup> Considering the fact that the majority of patients can be treated successfully by conservative means, surgical intervention mainly aims to acquire bacteriological or histological verification when CT-guided biopsy is inconclusive.<sup>37</sup> However, a surgical operation may also be necessary to drain enlarged abscesses,<sup>100</sup> despite the fact that sufficient drainage can be achieved with a CT-guided percutaneous catheter. Surgical drainage, bone debridement and reconstruction are indicated when an anterior abscess is larger than 2.5 cm on radiographs.<sup>98</sup> Only 10% to 20% of adult patients with pyogenic spondylodiscitis require open surgery;<sup>61</sup> in children, surgical treatment is rarely indicated, as conservative treatment is effective in most cases.<sup>59</sup>

Principles of surgical treatment are important; surgery should aim for decompression of neurological deficits and reconstruction for spinal stability and deformities. Timing of surgical treatment is critical; surgical decompression should be done as an emergency in patients with spinal nerve or cord compression, as prognosis may be poor after 48 hours from the onset of symptoms and signs, despite some authors' claims of good results even after

long-term paralysis.<sup>101</sup> Septicaemia is also a surgical emergency.<sup>3</sup> Epidural abscesses should be treated before neurological impairment ensues.<sup>102</sup> Moreover, prolonged unsuccessful conservative treatment may compromise the remaining healthy bone stock, leading to major reconstructive operations.

Recommendations regarding optimal surgical management are controversial.<sup>65,88,98</sup> The main goals of surgery include prompt decompression and stabilisation, aggressive debridement and tissue sample harvesting.<sup>65</sup> There is a wide spectrum of surgical options, including anterior, posterior or combined approaches and single-stage or two-stage procedures, with or without instrumentation. Less invasive endoscopic techniques for debridement and reconstruction have also been described. However, open surgery remains the standard of care, particularly in cases of extensive bone destruction.<sup>103</sup> Due to lack of specific guidelines for the optimal technique, surgeons often come to a decision taking into account the general health status, the most suitable spinal approach and instrumentation tailored to the characteristics of each patient and the individual surgeon's preference.<sup>7</sup>

Because spinal infections commonly involve the vertebral body, an anterior surgical approach decompression and debridement via an anterior approach, followed by anterior fusion is usually recommended.<sup>61</sup> After debridement, strut grafting with autografts, allografts or cages has been reported to be safe, provided that most of the infected tissue has been removed.<sup>104-106</sup> However, anterior fusion alone does not result in primary stability and when applied should be followed by prolonged bed rest and bracing. Additionally, in multi-segmental lesions, high rates of complications such as pseudarthrosis, graft displacement and spinal deformity have been reported.<sup>107</sup> For this reason, supplementary posterior stabilisation is usually required.<sup>98</sup> A posterior approach is preferred in the presence of an epidural abscess in the lumbar spine.<sup>98,108</sup> The posterior elements should not be destabilised by laminectomy alone.<sup>88</sup> Abscess drainage without fusion has been suggested in some reports,<sup>109</sup> but it may result in further instability and neurological deterioration. Consequently, a transpedicular instrumentation is usually advised.<sup>98</sup> Nevertheless, in some cases, an additional posterior approach is necessary for the correction and preservation of the sagittal alignment and augmentation of the stability of the affected segments.<sup>110,111</sup> Finally, posterior percutaneous instrumentation has been also postulated to be safe and effective in relieving pain, preventing deformity and neurological compromise in non-complicated cases involving the lower thoracic or lumbar spine.<sup>112,113</sup>

In the cervical spine, an anterior approach followed by grafting and plating may be performed. Locking plates with or without posterior stabilisation may be required in multilevel lesions.<sup>114</sup> In the thoracic spine, considering

that stability is maintained by the thoracic cage, a posterior approach with or without instrumentation is usually sufficient. An anterior approach alone may be effective for decompression and fusion in cases of single level involvement without posterior infectious spread.<sup>115</sup> In the presence of extensive anterior destruction and collapse, an anterior approach for debridement, decompression and fusion, followed by additional posterior instrumentation, is recommended.<sup>88,114</sup> If the thoracolumbar junction or lumbar spine is affected and the patient experiences neurological deficit or extended epidural infection, stabilisation is necessary after decompression. In cases of single segment disease with limited anterior involvement and minor kyphosis, an anterior fusion with bone grafts may be adequate.<sup>107</sup> Posterior lumbar interbody fusion with autologous iliac crest bone graft is also reported to be successful in cases of minor bone destruction.<sup>116</sup>

Instrumentation in the setting of infection constitutes a controversy in spinal surgery. Implantation of metallic implants into the infected site carries the risk of colonisation and persistent infection. However, a recent study recorded a higher re-operation rate after decompression alone compared with decompression with internal stabilisation.<sup>117</sup> Spinal instrumentation can be successful after thorough debridement and concomitant antibiotic administration.<sup>8,88,118</sup> Apparently, staphylococcal infections may heavily colonise spinal rods covering them with a thick biofilm, whilst only a few biofilm-covered colonies of *Mycobacterium tuberculosis* have been observed on stainless steel rods. These findings are in favour of anterior instrumentation at the time of surgical debridement, especially with titanium implants that have lower bacterial adherence.<sup>119</sup> Bone grafting seems to be safe even in the setting of an active infection,<sup>120</sup> with tri-cortical iliac autograft being usually the first choice. Structural allografts can also be used to avoid the associated donor site morbidity and to reduce operation time.<sup>121</sup> Titanium mesh cages also seem to be safe and successful for reconstruction after anterior debridement.<sup>122</sup> Pedicle screws are used in these cases to secure fixation. Finally, even if bacterial biofilm formation is reported to be more frequent with use of polyetheretherketone (PEEK) as compared with titanium in a laboratory setting,<sup>123</sup> recent reports advocate the use of PEEK cages for interbody fusion as a feasible and safe alternative.<sup>124,125</sup>

One-stage or two-stage procedure is another subject of debate, as risk of implant contamination by residual bacteria demands caution. In a study of patients with pyogenic and TB spondylodiscitis that received a two-stage procedure, advantages such as less operation time, less blood loss and safety for patients with poor general health have been reported.<sup>126</sup> In contrast, it has been reported that a single-stage procedure is a safe and efficient way to control infection and simultaneously reconstruct the

spine.<sup>127,128</sup> Both techniques seem to be efficient; however, two-stage operations increase hospital stay and the already compromised patients may not be able to withstand a second surgical procedure. The decision for the appropriate procedure should be based on surgical experience and general health status.

The Medical Research Council Working Party on Tuberculosis of the Spine, which was formed in 1963, designed the prospective multicentre clinical trials that took place in Hong Kong, Korea, Rhodesia and South Africa.<sup>129-138</sup> They studied various combinations of conservative treatments and compared conservative treatment to debridement alone, radical debridement and strut grafting. They described and popularised the 'Hong Kong operation', developed by Hodgson, that is thorough excision of the tuberculous focus, posteriorly as far as the dura mater, and cephalad and caudad, until healthy, bleeding cancellous bone is exposed, to create surfaces suitable for docking of a strut graft obtained from a cut rib.<sup>130</sup> They provided strict criteria for a favourable outcome for the patients, including no symptoms, full physical activity at work or school, no evidence of central nervous system involvement, no residual sinus or abscess detectable clinically or radiologically and radiographic evidence of healing of the spinal lesion.<sup>138</sup> In the short term, the Hong Kong operation provided faster bone union and resolution of abscesses compared with ambulatory chemotherapy, and similar results compared with debridement.<sup>132,135,138</sup> Additionally, in the long term, up to 15 years follow-up, the Hong Kong operation resulted in less kyphotic deformity, which is an important determinant not only of cosmetic well-being but also of possible future neurological impairment.<sup>139</sup>

## Strengths and weaknesses of the literature

A more recent literature review was published in 2016<sup>140</sup> and a second report using the GRADE approach<sup>141</sup> in order to obtain an evidence-based assessment of the literature on the management of patients with spondylitis (Table 1). From a total of 1662 related articles found in the four electronic databases, the systematic literature search for the purpose of that article resulted in 25 suitable included studies.<sup>140</sup> According to the GRADE approach, this systematic review concluded that 20 of the included articles had a very low level of evidence resulting in difficulty in producing definitive guidelines. Potential selection bias included inclusion of articles published only in the English language, articles published after 2000, exclusion of case reports and a small series focusing on a decision-making approach, and inherent limitations of the published studies such as the heterogeneity of the study populations with respect to age, gender, type of infections (pyogenic and TB; primary and post-operative) and

**Table 1. Summary of the most recent published studies on spondylodiscitis**

Study	Study design	Patients (number)	Type of infection	Positive cultures	Treatment	Antibiotics (duration)	Outcome	Follow-up (mean)
Hadjipavlou et al <sup>3</sup>	RCS	101	Pyogenic	75.5%	Conservative (57.4% required surgical treatment)	12 weeks	Relapse 2%, failure 0%, mortality 1%	Not given
Loibl et al <sup>25</sup>	RCS	105	Pyogenic TB (n=3)	56.2%	Conservative (53.3% required surgical treatment)	Not given	Mortality 12.4%	31.5 months
Legrand et al <sup>26</sup>	RCS	110	Pyogenic	72.8%	Conservative (brace, 89.1%)	103 days	Mortality 1%	3 months
Parra et al <sup>27</sup>	RCS	108	Pyogenic Postoperative (n=30) TB (n=11)	69.4%	Conservative (25% required surgical treatment)	5.2 weeks IV	Mortality 10%	73 months
Mulleman et al <sup>32</sup>	RCS	136	Pyogenic	100%	Conservative (brace, 74%; 8.9% required surgical treatment)	122 days	Mortality 4.6%	Not given
Kotil et al <sup>50</sup>	PCS	44	TB	100%	Conservative (4.6% required surgical treatment)	17 months	Favorable 95.4%	24 months
Hassan et al <sup>51</sup>	RCOMPS	42	TB	Not given	Surgical (anterior, n=20; posterior, n=22)	At least 2 weeks before and at least 9 months after surgery	Not given	15 months
Park et al <sup>52</sup>	RCS	116	TB	88.3%	Conservative (84.4% required surgical treatment)	6-9 months (n=20) vs > 12 months (n=96)	Favorable 70% vs. 83.3%	Not given
Jensen et al <sup>54</sup>	RCS	133	Pyogenic	40%	Conservative	2 to > 10 weeks	Relapse 10%, failure 14%, mortality 14%	Not given
Shi et al <sup>60</sup>	RCS	967	TB	100%	Conservative (76.5% required surgical treatment)	Not given	Relapse 0.6%, failure 0%, mortality 0%	Not given
Aagaard et al <sup>64</sup>	RCS	100	Pyogenic	90%	Conservative (41% required surgical treatment)	91 days	Relapse 4%, failure 0%, mortality 8%	12 months
Roblot et al <sup>91</sup>	RCOMPS	120	Pyogenic (n=98), Postoperative (n=22)	100%	Conservative	<6 weeks (n=36) vs. >6 weeks (n=84)	Relapse 0%, mortality 8% vs. relapse 7.1%, mortality 12%	6 months (n=120), 41 months (n=91)
Bernard et al <sup>92</sup>	RCT	351	Pyogenic	100%	Conservative	6 weeks (n=176) vs. 12 weeks (n=175)	Relapse 2.3%, failure 9.1%, mortality 8% vs. relapse 0%, failure 9.1%, mortality 7%	12 months
Valancius et al <sup>99</sup>	RCOMPS	196	Pyogenic	72.9%	Conservative (n=91) and surgical (n=105)	At least 2 weeks IV and 3-6 months per os	Relapse 7.6%, failure 13.1%, mortality 8.7% vs. relapse 2.9%, failure 0%, mortality 1.9%	12 months
Rosbach et al <sup>100</sup>	RCS	135	Pyogenic TB (n=8)	59.5%	Conservative (brace) and surgical (n=75)	Not given	Not given	Not given
Si et al <sup>105</sup>	PCOMPS	23	Pyogenic	Not given	Surgical (anterior, n=12; posterior fusion, n=11)	Not given	Relapse 0%, failure 0% vs. relapse 0%, failure 0%	38 months
Pee et al <sup>106</sup>	RCOMPS	60	Pyogenic	50%	Surgical (anterior cages and pedicle screw fixation, n=37; anterior struts and pedicle screw fixation, n=23)	At least 6 weeks IV and at least 6 weeks per os	Infection resolution in all patients	35.8 months
Vcelak et al <sup>108</sup>	RCOMPS	31	Pyogenic TB (n=4)	100%	Surgical (dorsal transmuscular, n=23; two-stage posterior-anterior, n=8)	Not given	Relapse 8.7%, failure 4.3%, mortality 4.3% vs relapse 0%, failure 0%, mortality 0%	12 months
Ozturk et al <sup>110</sup>	RCOMPS	56	Pyogenic TB (n=16)	100%	Surgical (sequential, n=29; simultaneous anterior and posterior surgery, n=27)	6 weeks IV and 3 months per os (pyogenic) 9 months (TB)	Failure 0%	78 months
Lee et al <sup>111</sup>	RCOMPS	26	Pyogenic TB (n=2)	42%	Surgical (transpedicular curettage and drainage, n=10; combined anterior-posterior approach, n=26)	91.1 days vs 65 days	Relapse 10%, failure 0%, mortality 0% vs relapse 0%, failure 0%, mortality 0%	57 months
Nasto et al <sup>112</sup>	RCOMPS	27	Pyogenic	100%	Conservative (brace, n=15) and surgical (n=12)	76-84 days	Relapse 0%, failure 0%, mortality 0%	9 months
Lin et al <sup>113</sup>	RCOMPS	45	Pyogenic	84%	Surgical (combined anterior-posterior, n=25; combined anterior-percutaneous posterior, n=20)	28-83 days	Relapse 8%, mortality 0% vs relapse 5%, mortality 0%	24 months
Karadimas et al <sup>117</sup>	RCS	163	Pyogenic TB (n=22)	59%	Conservative (brace, n=70) and surgical (without, n=56; with instrumentation, n=37)	2-7 months	Failure 0%, mortality 11.4% vs. failure 12.5%, mortality 13.5%	12 months
Pourtaheri et al <sup>118</sup>	RCOMPS	104	Pyogenic	Not given	Surgical (instrumented, n=57; non-instrumented, n=47)	Not given	Infection resolution 54%, mortality 9% vs. infection resolution 42.5%, mortality 17%	43 months
Schomacher et al <sup>125</sup>	RCOMPS	37	Pyogenic	70.3%	Surgical (PEEK cages, n=21; titanium cages, n=16)	2-4 weeks IV, 8-10 weeks per os	Reinfection was not observed in any patient	20.4 months
Chen et al <sup>128</sup>	RCS	24	<i>Brucella</i>	100%	Surgical (posterior debridement, bone grafting and instrumentation)	6.5 months	Infection resolution	14.3 months
Linhardt et al <sup>143</sup>	RCT	22	Pyogenic TB (n=5)	Not given	Surgical (ventro-dorsal spondylodesis, n=20; ventral spondylodesis, n=10)	23.8-24.1 weeks	Relapse 8%, failure 0%, mortality 25% vs relapse 0%, failure 0%, mortality 10%	63 months

Note: TB: tuberculosis; RCS: retrospective case series; RCT: randomized controlled trial; RCOMPS: retrospective comparative study; PCS: prospective comparative study; PEEK: poly-ether ether ketone

treatments, and small sample sizes.<sup>140</sup> However, there was a strong level of recommendation for six weeks of systemic antibiotic treatment in uncomplicated pyogenic spondylodiscitis, as shown in one randomised control trial (RCT),<sup>142</sup> and a strong level of recommendation that, if surgical treatment is indicated, an isolated anterior approach can result in better clinical outcomes compared with more extensive combined anteroposterior procedures, as shown in a prospective comparative study<sup>105</sup> and a RCT.<sup>143</sup> This study concluded that a prognostic systematic review regarding the effect of patient characteristic on the outcome of spondylodiscitis could be a valuable addition to the available literature, and that emerging less invasive surgical techniques should be studied more extensively.<sup>140</sup>

## Conclusion

Spondylodiscitis may involve the vertebral bodies, the intervertebral disc, the paravertebral structures and the spinal canal with potentially high morbidity and mortality rates. The incidence has risen in recent years due to an increase in the susceptible population and an improved diagnostic accuracy with advanced imaging. However, diagnosis remains challenging because the disease may have an insidious onset, with subtle and misleading clinical features. The management of spondylodiscitis requires a multidisciplinary approach involving radiologists, infectious diseases specialists, spine surgeons and rehabilitation personnel. Conservative treatment is the basic standard of care. Surgical treatment via an anterior and/or posterior approach, in the setting of a one- or a two-stage procedure, with or without instrumentation, may be needed occasionally. Unfortunately, the majority of the published studies have a low level of evidence, with very few studies showing strong levels of recommendation for a treatment approach. Therefore, further research is necessary to provide high levels of evidence for the management of patients with spondylodiscitis.

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