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REVIEW ARTICLE

Infections of the spine: Current concepts and a literature review

Gavriil P., Sioutis S., Bekos A., Gerasimides P., Georgoulis J., Soultanis K., Mavrogenis A.F., Sapkas G.
First Department of Orthopaedics, National and Kapodistrian University of Athens, School of Medicine, ATTIKON University Hospital, Athens, Greece

ABSTRACT

Infections of the spine comprise a wide spectrum of different clinical manifestations depending on the exact anatomical structure involved. Spinal infections pose an essential health problem, the treatment of which requires a multidisciplinary approach. Diagnosis is based on clinical symptoms, radiologic evidence, laboratory tests and biopsy. The most common pathogens are bacteria; most of which spread hematogenously. Current treatment involves a combination of antibiotic agents. Sometimes, surgery is required to eradicate the infection or to treat its complications. In all cases, thorough and repetitive clinical examination and laboratory tests are of paramount importance for optimal outcomes.

KEY WORDS: Spine Infections, Spondylitis, Spondylodiscitis, Pathogenesis, Clinical Presentation, Back pain

1. Introduction

Infections of the spine and their various clinical manifestations consist a group of challenging medical conditions which necessitate a team of specialists for optimal diagnosis, treatment and recovery. The responsible pathogens are usually bacteria, however, fungi and even parasites can be encountered. Spinal infections can be classified as pyogenic (bacterial), granulomatous (tuberculosis or fungal) or parasitic (Echinococcosis).[1] Alternatively, an anatomical classification can be used. [2]. Depending on the route of spread of the pathogens, spinal infections can be divided in those that spread hematogenously, from adjacent tissues, or through direct inoculation. This is a review of the literature regarding infections of the spine. We also describe and summarize the epidemiology, pathogenesis, clinical manifestation, diagnosis and management of spinal infections.

2. Epidemiology

Spinal infections are relatively rare with an estimated incidence around 22 cases per million per year. [3] Vertebral osteomyelitis is responsible for about 0.15% to 5% of all osteomyelitis cases.[4] Despite being a rare entity, vertebral osteomyelitis is the most frequent form of osteomyelitis spreading hematogenously in older patients. [5]

The most commonly diagnosed spinal infection is primary pyogenic spondylodiscitis [2],[6]. The causative pathogens are Gram positive bacteria especially Staphylococcus Aureus.[7] The disease has a male: female ratio of 1.5.[3],[8] It usually affects people in their 50s or 60s.[9] An exception is younger intravenous drug users.[10] Prior to the use of antibiotics, spondy-

CORRESPONDING AUTHOR, GUARANTOR

Mavrogenis A.F., Associate Professor, First Department of Orthopaedics, National and Kapodistrian University of Athens, School of Medicine, ATTIKON University Hospital, Athens, Greece, Mob.: 697 222 60 96
E-mail: afm@otenet.gr, andreasfmavrogenis@yahoo.gr

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lodiscitis had a mortality ratio of 25–71%. The current rate is 2–12% [11]

The spine can be extensively affected with multifocal or adjoining lesions (common in TB osteomyelitis) or present as an isolated site of infection as in pyogenic cases. [12] The most common region affected is the lumbar spine followed by the thoracic spine. [4], [6] A distinct entity, tuberculous spondylodiscitis has predilection for the thoracolumbar region.[13] Sacral osteomyelitis has been described, usually as a complication of infected pressure ulcers in bedridden patients.[14] The infection may expand posteriorly forming epidural or subdural abscesses, or laterally, forming most commonly psoas abscesses.[15] Facet involvement has been described as septic facet joint arthritis.[16]

In terms of epidemiology, certain risk factors predispose to spinal infection; immunocompromised in particular are in great danger.[5] Another category, intravenous drug addicts incur high likelihood of infection from repetitive injections.[10] Likewise, people with common clinical conditions like diabetes, malignancy, renal or hepatic failure sustain a higher risk for spinal infection.[17],[18] A distinct category of patients with increased likelihood for regional infection are those who had spinal surgery and those with orthopedic or other implants.[19] Moreover, immigrants from third world countries, inmates, and those of low socioeconomic level are exceptionally vulnerable. [20]

3. Pathogenesis

There are two possible routes of dissemination: the hematogenous and the non-hematogenous; the latter is further divided to direct inoculation and contiguous spread. In hematogenous spread bacteria due to simple events like tooth brushing related microtrauma or more serious, like urinary tract infections circulate in the bloodstream.[21] A common source of bacteremia are various kinds of medical implants. Hematogenous spread allows bacterial seeding the metaphysial and cartilaginous end-plates and afterwards into the adjacent tissue.[22] The characteristic vascular anatomy and physiology of the region provides the appropriate circumstances (slow blood flow, lack of valves) for pathogen adherence and proliferation. The hematogenous route is the most common route of dissemination and perfectly describes the pathogenesis of pyogenic spondylodiscitis. Once microorganisms enter the vascular arcades in the metaphysis, the infection spreads. The disc is destroyed by bacterial enzymes.[23] Tuberculous infection stems from Batson's paravertebral venous plexus. Tuberculous spondylitis characteristically encompasses early obliteration of the anteroinferior part of vertebral bodies and may then expand beneath, involving the anterosuperior aspect of the inferior vertebra.[12] However, tuberculous spondylitis does not destroy the disc until late disease.[24].

There are two additional, less frequent, ways of pathogen dissemination in spinal infection. The first is direct inoculation, commonly due to regional trauma or recent surgery in the spine or surrounding tissue. [25],[26] The second is contiguous spread from adjacent foci as the aorta, the esophagus or the bowel.[27]

Children and adults manifest differences regarding pathogenesis. In children, the spread of infection is rapid, because vessels supply both the end plates and the intervertebral discs, whereas in adults, intra-osseous arteries are end-arteries; septic emboli may occlude the circulation, resulting in broad destruction. [28]

4. Clinical presentation

Awareness of the clinical presentation is crucial in the recognition of spinal infection.[29] Nonetheless, this can be particularly difficult due to the non-specific, and often mild symptoms of spondylodiscitis, especially in early disease. Thus, initial diagnosis delays more than three months after development of the first symptoms in about 50% of the patients. [30]

Idiopathic back or neck pain has often been described as the predominant symptom.[31] Paravertebral muscle tenderness and spasm, and limitation of spine movement represent the predominant signs in spondylodiscitis. [32] Pain should be differentiated from the common back pain. This can be achieved by looking for concomitant "red flags", for instance fever, malaise, neurological deficits, and persistent symptoms with minimum or no improvement. However, fever is rarely present in patients with mycobacterial, brucella, or fungal spondylodiscitis and may be absent in patients taking analgesics.[33]

Clinical examination is necessary and can be very helpful. Inspection of the patient can detect the cause

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TABLE 1.

Table 1: Parenteral Antimicrobial Treatment of Common Microorganisms Causing Native Vertebral Osteomyelitis (Ryang, Y.-M., Akbar, M., 2020.)

Microbiology [77], [78]	Incidence (%)	Route of infection
Staphylococcus aureus	20–84	Most common pathogen; 1.7–6% of bloodstream infections complicated by VO
Coagulase-negative staphylococci	5–16	Device-related bacteraemia or direct inoculation in post-operative infections
Streptococci and enterococci	5–20	Haematogenous spread. Associated with infective endocarditis in 26%
Enterobacteriaceae	7–33	Haematogenous spread from urinary tract infections in older population. Commonly Escherichia coli, Proteus, Klebsiella, Enterobacter spp
Anaerobes	<4	Contiguous spread from pelvic or intra-abdominal foci. Cutibacterium acnes direct inoculation from implants
Polymicrobial	<10	Contiguous spread

(scars due to trauma or previous operations). Paravertebral tenderness and masses (muscle spasm or rarely abscess formation) may be palpated. [34]

The role of neurologic examination is crucial because it can unveil neurologic deficits. In such cases, common findings are muscle weakness, sensory impairment or loss and sphincters incompetence.[54]

5. Diagnosis

Any delay in diagnosis increases the risk for abscess formation and confer increased morbidity and mortality.[29] Co-existing medical conditions, previous surgeries and drug use can raise the suspicion for spinal infection or elucidate the primary cause. [11],[18]

Laboratory work up includes White Blood Cells count (WBC), Erythrocyte Sedimentation Rate (ESR) and C - reactive protein (CRP). WBC is slightly elevated or normal in about half the patients with spondylodiscitis, thus is relatively nonspecific. ESR is a more sensitive inflammatory marker, found elevated in > 90% of patients.[36] CRP seems to be the most important blood test, being very sensitive and normalizing in response to treatment.[35] However, these markers remain relatively nonspecific.[37] Blood cultures should be part of routine laboratory evaluation. However, cultures often fail to identify a specific pathogen. [38] Quantification of interferon-gamma (IFN-γ) based tests for tuberculous infection detection or serologic tests for Brucella can be utilized in patients from endemic areas.[39]

The next step is the use of radiologic modalities. Even though radiographs have low specificity, they remain a valuable, low-cost, diagnostic tool with high sensitivity.[40] Radiographic signs suggesting spondylodiscitis are narrowing of disc space, loss of definition and irregularity of the vertebral endplate. Pedicle, lamina and spinous process involvement is rare in pyogenic spondylodiscitis and should alert for tuberculous infection. [41] Destruction of intervertebral disc is indicative of pyogenic infection.[4], [42]

MR imaging is the modality of choice with 96% sensitivity, and 94% specificity.[43],[44],[45] MRI offers details about paravertebral soft tissue involvement, abscess formation, nerve root and spinal compression. Although gadolinium-enhanced MRI scans are highly sensitive and specific they often overestimate the presence and extent of infection. [46]

Computerized Tomography (CT) can be utilized whenever MRI is contraindicated. Indicative findings of vertebral infection are end-plate erosion, paravertebral fat reduction, disc hypodensity and bone necrosis or pathological calcification. [37], [42]

Technetium or leucocyte labelled bone scintigraphy, although relatively sensitive (90%), has low specifity,

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TABLE 2.

Parenteral Antimicrobial Treatment of Common Microorganisms Causing Native Vertebral Osteomyelitis (Barberi et al., 2015)

Microorganism	First Choice[a]	Alternatives[a]	Comments[b]
Staphylococci, oxacillin susceptible	Nafcillin[c] sodium or oxacillin 1.5–2 g IV q4–6 h or continuous infusion or Cefazolin 1–2 g IV q8 h or Ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h[d] or daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin 500–750 mg PO q24 h and rifampin PO 600 mg daily [86] or clindamycin IV 600–900 mg q8 h	6 wk duration
Staphylococci, oxacillin resistant [87]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6–8 mg/kg IV q24 h or linezolid 600 mg PO/IV q12 h or levofloxacin PO 500–750 mg PO q24 h and rifampin PO 600 mg daily [86]	6 wk duration
Enterococcus species, penicillin susceptible	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses; or ampicillin sodium 12 g IV q24 h continuously or in 6 divided doses	Vancomycin 15–20 mg/kg IV q12 h (consider loading dose, monitor serum levels) or daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of therapy. Optional for other patients [88], [89]. Vancomycin should be used only in case of penicillin allergy.
Enterococcus species, penicillin resistant[e]	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	Daptomycin 6 mg/kg IV q24 h or linezolid 600 mg PO or IV q12 h	Recommend the addition of 4–6 wk of aminoglycoside therapy in patients with infective endocarditis. In patients with BSI, physicians may opt for a shorter duration of aminoglycoside. The additional of aminoglycoside is optional for other patients [88], [89]
Pseudomonas aeruginosa	Cefepime 2 g IV q8–12 h or meropenem 1 g IV q8 h or doripenem 500 mg IV q8 h	Ciprofloxacin 750 mg PO q12 h (or 400 mg IV q8 h) or aztreonam 2 g IV q8 h for severe penicillin allergy and quinolone-resistant strains or ceftazidime 2 g IV q8 h	6 wk duration Double coverage may be considered (ie, β-lactam and ciprofloxacin or β-lactam and an aminoglycoside).

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Enterobacteriaceae	Cefepime 2 g IV q12 h or ertapenem 1 g IV q24 h	Ciprofloxacin 500–750 mg PO q12 h or 400 mg IV q12 hours	6 wk duration
β-hemolytic streptococci	Penicillin G 20–24 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration Vancomycin only in case of allergy.
Propionibacterium acnes	Penicillin G 20 million units IV q24 h continuously or in 6 divided doses or ceftriaxone 2 g IV q24 h	Clindamycin 600–900 mg IV q8 h or vancomycin IV 15–20 mg/kg q12 h (consider loading dose, monitor serum levels)	6 wk duration Vancomycin only in case of allergy.
Salmonella species	Ciprofloxacin PO 500 mg q12 h or IV 400 mg q12 h	Ceftriaxone 2 g IV q24 h (if nalidixic acid resistant)	6–8 wk duration

Abbreviations: BSI, bloodstream infection; IV, intravenous; PO, take orally; q, every.
[a] Antimicrobial dosage needs to be adjusted based on patients' renal and hepatic function. Antimicrobials should be chosen based on in vitro susceptibility as well as patient allergies, intolerances, and potential drug interactions or contraindications to a specific antimicrobial.
[b] Recommend Infectious Diseases Society of America guidelines for monitoring of antimicrobial toxicity and levels [136]
[c] Flucloxacillin may be used in Europe.
[d] Vancomycin should be restricted to patients with type I or documented delayed allergy to β-lactams.
[e] Daptomycin, linezolid, or Synercid may be used for vancomycin-resistant enterococci.

thus it is not routinely used. A plethora of novel nuclear imaging modalities exist such as 111 In, Gallium spine scan and strepteridin scintigraphy. These modalities are very sensitive and specific, however, the requirement for specialized facilities and personnel, limits their role.[47],[48],[49] Fluorine-18 (F-18) fluorodeoxyglucose-positron emission tomography (FDG-PET) has shown promising results for both acute and chronic infection, being particularly useful in patients with metallic implants because FDG uptake is not hampered by metallic artifacts.[50], [51]

When blood cultures fail to identify a pathogen, biopsy is considered; open or percutaneous. While open biopsy is a last resort option, percutaneous biopsy is routinely executed.[52],[53],[54] In addition to bacterial cultures, mycobacterial, brucella and fungal cultures should be obtained.[55], [56] If the results are inconclusive, a second CT-guided needle biopsy may be performed before open biopsy is finally required.[57] In either case PCR should be used. Molecular diagnostic tools have improved the yield of microbiologic diagnosis via tissue biopsy.[58],[59] Use of antimicrobial agents before biopsy remains a highly debatable topic. We recommend adhering to the classical approach and withholding initiation of treatment when this is feasible.[60],[61],[62] In patients with neurologic compromise or hemodynamic instability, we recommend immediate surgical intervention plus empiric antimicrobial therapy.[63]

6. Differential diagnosis

Diagnosis of spinal infection based on clinical signs and symptoms is very challenging. Initial differential diagnosis consists of common causes of back and neck pain such as trauma, disc herniation, osteoporosis, rheumatic diseases and pathologic conditions as malignancies.

A distinction between mechanical causes and pathologic conditions can be presumed clinically. Back pain that resolves with bed rest and limitation of physical activity points towards mechanical causes. On the other hand, pain of insidious onset with evolving neurologic deficits, prolonged pain, aggravating at night or with rest and accompanied by other general signs and symptoms should raise awareness for pathologic conditions. Imaging and biochemical, microbiological and histopathological evaluation should be considered.

7. Microbiology

Epidemiology of the causative pathogens of spinal in-

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fections varies. Vertebral osteomyelitis can be polymicrobial, albeit usually one pathogen is responsible.[23] The infectious microorganisms are bacteria, fungi or rarely parasites; bacteria remain the predominant cause of the disease. Specifically, gram positive cocci are responsible for the most common type of spinal infection: pyogenic vertebral osteomyelitis, whereas in the past, tuberculous osteomyelitis was the commonest.[64] Although uncommon in Western world nowadays, TB remains an important cause of spinal infection in endemic countries. Patients with tuberculous spinal infection, not coming from an endemic area typically are immunocompromised or elders, possibly reflecting reactivation of a latent infection.[65] In extreme cases, spondylodiscitis is a complication of intravesical BCG (bacillus Calmette-Guerin) instillation in people treated for bladder cancer.[66] Staphylococcus aureus is the most common isolated bacterium, responsible for 20% to 84% of all spinal infections.[7],[67] Staphylococcus lugdunensis has been associated with deep-seated infections and may mimic S. aureus.[68] Staph. Epidermitis, related with iatrogenic or periprosthetic infection, has been linked with cases of spondylodiscitis.[69] Streptococci and Enterococci related spinal infections represent 5% to 20% of cases.[40] Enterobacteriae species follow with about the same incidence (7-33%). They are strongly related with concomitant urinary tract or gastrointestinal infections. Salmonella species have been linked with vertebral osteomyelitis in children, particularly those with sickle cell disease[70] . Another causative pathogen for spinal infection in children is Kingella Kingae, however, it is not routinely isolated. [71] Pseudomonas aeruginosa, a rare pathogen, is found in 0% to 6% overall positive bacterial cultures.[72],[73] IV drug abusers are more likely to be infected with Pseudomonas.[74] Cutibacterium Acnes has been implicated as causative pathogen for spinal infection, despite previously considered iatrogenic contaminant. Implant associated contamination during orthopedic surgeries is another way of seeding.[75],[76]

Brucella species should be considered in endemic areas, accounting for 30% of spinal infections.[3], [79],[80] Fungal spinal infection is rare and can occur in patients in endemic areas or certain host risk factors such as immunocompromised (Aspergillus), intravenous drug users or indwelling intravenous catheters (Candida, Aspergillus). [81],[82] Parasitic infections are extremely rare globally but common in endemic areas. Specifically, spinal echinococcosis, due to Echinococcus granulosus, is found in sheep breeding areas of the Eastern and Southern countries of Mediterranean sheep breeding. Thus, awareness and clinical suspicion is necessary in patients coming from these regions.[83]

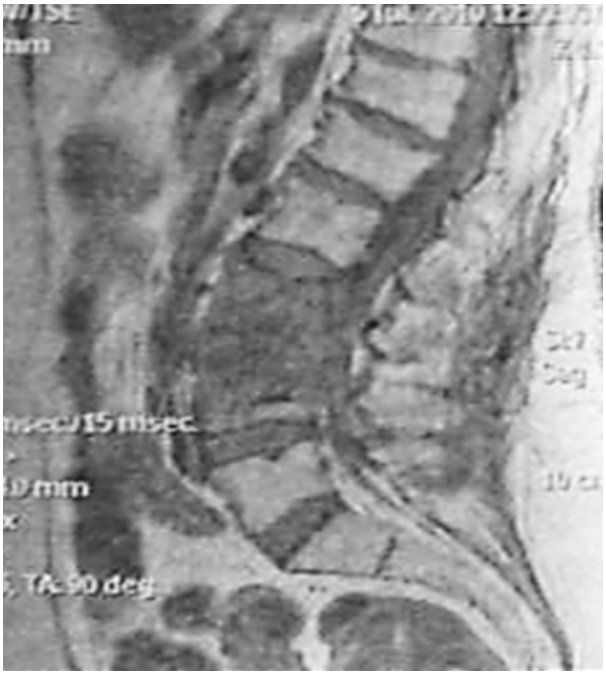

Figure 1. *Pyogenic spondylitis of the L3 and L4 vertebrae after facet joint ingections successfully treated with debridement and antibiotics.*

8. Conservative treatment

The next step is appropriate therapeutic management. Conservative treatment is the treatment of choice in uncomplicated spondylodiscitis and those who are not candidates for surgical operation. Conservative treatment involves antibiotics, analgesics, special spinal braces, physiotherapy and immobilization. The goal is pain suppression, infection eradication and ensuring the stability of the vertebral column.[84]

Regarding immobilization, usually a period of bed rest (1-2 weeks) followed by a period of patient ambulation using special rigid braces is applied. Prolonged bed rest (up to six weeks) is associated with complications such as thrombi and pulmonary emboli, thus should be applied only when necessary. Generally, early ambula-

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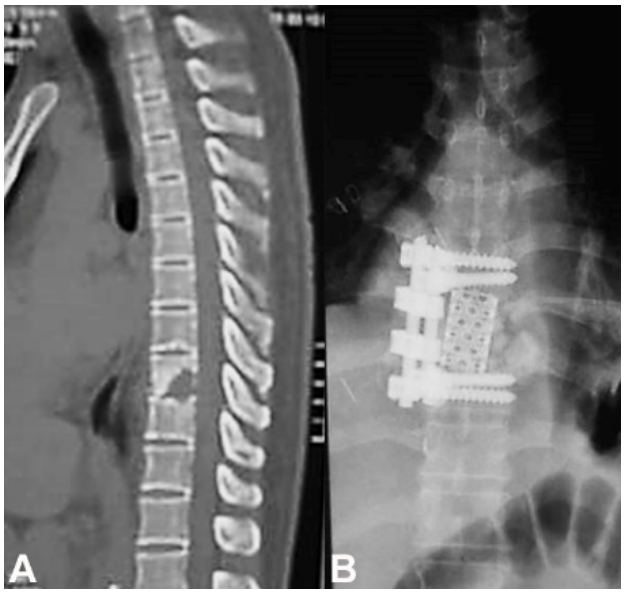

Figure 2. *(A) TBC spondylitis of the T9 vertebra (B) successfully treated with vertebrectomy and fusion, and antituberculous medication for 12 months.*

tion with spinal braces should be encouraged. [85]

Antibiotics are used invariably in the clinical management of patients with spinal infection. Generally, in patients with hemodynamic instability, progressive or severe neurologic symptoms empirical antimicrobial therapy is initiated, whereas in stable patients selective antimicrobial therapy based on the specific pathogen and susceptibility tests is applied.[61] According to IDSA 2015 guidelines, empiric regimen should cover for staphylococci, including MRSA, streptococci, and gram-negative bacilli. Such regimens include a combination of vancomycin and a third- or fourth-generation cephalosporin. In case of allergy or intolerance, daptomycin and quinolone are reasonable alternatives.[23] Common therapeutic regimen are shown in the following table:

Treatment of spinal tuberculosis necessitates a complicated combination of antimicrobial agents.[91] A commonly used protocol constitutes of isoniazid, rifampicin, ethambutol, and pyrazinamide.[92] Brucella spondylodiscitis is treated with a combination of either streptomycin plus doxycycline or rifampin plus doxycycline.[11] Management of patients with fungal spinal infection involves a variety of drugs; azoles and amphotericin B are the most common choices.[93],[94]

Prolonged antibiotic treatment is recommended due to the limited bone penetration of most antimicrobials. [95],[96] Nevertheless, the optimal duration remains a debatable topic with most studies suggesting a 6-8 week regimen.[97] Accordingly, the 2015 IDSA guidelines recommend a 6 week antibiotic therapy.[23] This is mainly based on a randomized clinical trial that showed that 6 weeks of antibiotic treatment is noninferior to 12 weeks. The 6-week recommendation is, also, supported by another retrospective study in which the first group was treated for less than 6 weeks and the second for more than 6 weeks. The outcomes, rates of relapse and deaths were comparable between the two groups.[84]

Treatment can be discontinued after 6 weeks in most patients with clinical improvement. However, those diagnosed with Brucella, Tuberculous or fungal infection should continue their therapy for the targeted duration.[4],[98] In case of complications such as abscess formation, the duration of treatment is prolonged.[99] Pediatric patients should receive intravenous antibiotics for about two weeks, followed by oral antibiotic for another one to three weeks if there is clinical and laboratory improvement.[99]

There is controversy regarding the switch from parenteral drug administration to oral. Intravenous antibiotics are used initially for 2 to 4 weeks in most cases. [30], [100] Recent studies argue that an early switch to agents with great oral bioavailability has similar efficacy to prolonged intravenous drug administration. [62],[101]

Discontinuation of antimicrobial therapy is considered in neurological deterioration with imaging tests indicating progressive destruction. Furthermore, a different approach should be considered if the expected clinical improvement is not achieved.[100] In either case, attempts to isolate a pathogen should be made.

9. Surgical management

A surgical approach is deemed necessary in case of failure of conservative measures.[102] Other indications for surgery are symptoms persistence, onset or progression of neurologic deficits, spinal instability, abscess larger than 2.5 cm, signs of ischemia or compression and deformities such as kyphosis or scoliosis. [103],[104] Urgent operation is indicated in septicemia

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TABLE 3.

Criteria for absolute and relative surgery indications. (Saeed et al., 2019)

Indication for surgery	Absolute	Relative
Neurologic deficit	+	-
Spinal instability/ deformities (e.g. Kyphosis)	+	-
Spinal core compression/ cauda equina	With neurologic deficit	Without neurologic deficit
Space occupying/ non drainable abscess	+	-
Sepsis	+	-
Conservative treatment failure	-	+
Extensive spread of the infection	Antibiotics non responsive, clinical, laboratory, imaging deterioration with positive cultures	Without laboratory and clinical deterioration

or rapid clinical deterioration with no response to drug treatment.[30],[99]

Thorough surgical debridement and maintenance or restoration of vertebral stability are the principal goals. Open surgery with extensive debridement of the infected tissue is most times recommended while minimally invasive surgery is an alternative method. [105]

Anterior approach is indicated for anterior debridement and stabilization ,whereas the posterior approach is indicated for decompression of a primary posterior epidural abscess with concomitant posterior spinal instrumentation.[106] A combined anterior-posterior approach has been occasionally used.[105],[107]

Thorough debridement may result in extensive tissue loss endangering the vertebral column's integrity. Therefore, instrumentation and bone grafting are used to stabilize the spine. However, some authors believe that metallic implants are possible foci for bacterial adherence.[103] Nevertheless, spinal instrumentation provides stability and increased fusion rates.[107] Moreover titanium alloy implants are less prone to colonization than stainless steel ones. [108] Additionally, less time of patient immobilization is required. [109]

In postoperative spinal infections with metallic implant involvement, implant removal is most times mandatory.[67] However, stable grafts adherent to native bone should be left in place. If implant removal results in fracture of the fusion mass, bone grafting should be done to ensure alignment of the vertebral column.[110]

10. Conclusion

Spinal infection is a well-documented disease which predominantly affects people with certain risk factors and people from endemic areas. The most common pathogens are bacteria, especially Staphylococcus species. Diagnosis is quite challenging, requiring collaboration of physicians from different fields of medicine. Appropriate management remains an area of controversy. Most evidence-based guidelines along with experts' opinion recommend a conservative approach of antimicrobial drugs and patient immobilization. Surgical treatment may be considered in infection persistence, and extensive disease. Surgery involves broad debridement, bone grafting and spinal stabilization. Publication of more studies is crucial to ensure optimal diagnostic evaluation and disease management.

Conflicts of Interest

The authors declare that they have no conflicts of Interest.

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