EJMA

DOI: 10.14744/ejma.2022.08370
EJMA 2023;3(2):61–66

Review

Infectious Spondylodiscitis, an Overlooked Cause of Pain: A Review

Aysel Çınar Sayhan

Department of Physical Medicine and Rehabilitation, Bilecik Research and Training Hospital, Bilecik, Türkiye

Abstract

Infectious spondyloarthritis occurs through the transmission of a microorganism by various routes, causing an infection in the spine. It can be diagnosed on any desired MRI based on clinical suspicion in the presence of an appropriate clinical manifestation (fever, pain, loss of strength) along with a significant increase in leukocyte, Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP) laboratory parameters. The definitive diagnosis is made by demonstration of the microorganism in the biopsy material. Since the disease is rare and low back pain is very common in the population, the diagnosis is often missed and delayed.[1] Therefore, it still remains an important cause of comorbidity. Delayed diagnosis of this disease, which can be treated with appropriate antibiotic therapy, may result in disability by causing neurological sequelae.[2]

The aim of this review is to provide information about infectious spondylodiscitis at a level to manage the diagnosis, treatment, and follow-up process, to keep this diagnosis in mind in patients with risk factors who present with back pain and local tenderness in the spine, especially in patients from endemic regions of tuberculosis and brucellosis, and to expand the investigation in this direction.

Keywords: Brucellosis, infectious spondyloarthritis, spondyloarthritis, tuberculosis

Cite This Article: *Çınar Sayhan A. Infectious Spondylodiscitis, an Overlooked Cause of Pain: A Review. EJMA 2023;3(2):61–66.*

Spondylodiscitis refers to inflammation of the vertebral body and intervertebral discs. The infection arises as osteomyelitis of the subchondral bone and spreads to the intervertebral disc. Spinal infections present with different characteristics and clinical manifestations. These include pyogenic (bacterial), granulomatous (tuberculous or fungal), or parasitic (Echinococcosis) infections. The incidence is increasing with the increase in spinal surgery and the longer life expectancy of elderly patients with chronic diseases.[3]

The main pathogenic organisms are staphylococci and Mycobacterium tuberculosis. Staphylococcus aureus is the cause of infection in more than half of the patients.[4] The lumbar region (56%) is most commonly involved, followed by the thoracic region (35%). It is more common in men over the age of 60 years and in early childhood. It can be transmitted by hematogenous spread, contiguous spread, and direct inoculation. The contiguous spread usually occurs after infections of the thoracic and intra-abdominal organs. Risk factors include recent or current diseases, diabetes mellitus, rheumatoid arthritis, steroid use, intravenous drug use, alcohol and substance abuse, and a recent history of surgery.

Clinical Features

The major symptoms of spinal infections are pain, fever, and loss of muscle strength. The most common symptom

Address for correspondence: Aysel Çınar Sayhan, MD. Department of Physical Medicine and Rehabilitation, Bilecik Research and Training Hospital, Bilecik, Türkiye
Phone: +90 554 391 74 73 **E-mail:** doktoraysel51@gmail.com

Submitted Date: November 09, 2022 **Revision Date:** November 09, 2022 **Accepted Date:** December 15, 2022 **Available Online Date:** October 27, 2023

is low back pain. Constitutional symptoms such as night sweats, weakness, and weight loss may also be seen. Pain is of inflammatory characteristic. It does not relieve with rest, wakes the patient up at night, and is unresponsive to painkillers. Patients always maintain the same posture in order not to increase pain. Since standing upright increases the pain, those with infections in the lumbar and thoracic region have almost a crouch gait pattern. Those with infection in the cervical region hold their head with their hands to minimize movement. They walk with minimal steps without turning left or right. This gait and posture are typical for spinal infections. In patients presenting with pain, typical gait and posture can guide us in this way while making a diagnosis. If the infection has involved soft tissues, there may be local tenderness on the involved vertebra. The infection may spread anteriorly and the paravertebral abscess may extend posteriorly, forming an epidural abscess. Due to large paravertebral abscesses, the pain may radiate to the legs, abdomen, scrotum, and perineum.

Fever is usually mild if any. It may be elevated in children during the septicemia period. If fever rises at night and is accompanied by night sweats, care should be exerted for tuberculosis. On the other hand, relapsing high fever is seen in brucellosis.[5] While postoperative early fever suggests atelectasis and pulmonary embolism, deep infections such as spondylodiscitis should be considered in a high fever that occurs months after the operation.

Approximately 10-50% of patients develop neurological loss. The occurrence of neurological deficit is usually due to the epidural abscess. The abscess can spread directly or the bacteria can reach the neural elements through the spinal canal. In fractures caused by softening of the bone after infection, compression may result in neurological deficits.

Physical examination reveals severe pain in active or passive range of motion of the spine. Loss of muscle strength is detected in those presenting with neurological deficits.

Diagnosis

The diagnosis is usually delayed because the disease is not considered initially. The average time to diagnosis is as long as 3 months. Initial laboratory tests should include investigation of inflammatory parameters such as leukocyte count, ESR and CRP, blood and urine culture, and brucella and tuberculosis tests. Conventional radiographs are taken. The time to the emergence of signs of infection on direct X-ray ranges from 2 to 4 weeks. Therefore, contrast-enhanced magnetic resonance imaging (MRI) should be performed for suspected patients or those with positive findings. The first radiological finding is blurring of the endplates. Narrowed disc space, corpus destruction, and decreased intervertebral body height can be noted. Bone marrow changes on both sides of the intervertebral disc on MRI are typical findings for infectious spondylitis. The earliest MRI finding is bone marrow edema in the vertebral body. Bone marrow edema is visualized as hypointense on T1W images, hyperintense on T2W images, and hyperintense on fat-suppressed T2W images. MRI is the diagnostic technique of choice for spondylodiscitis. Moreover, it is the most advantageous technique in the diagnosis of spondylodiscitis.[6] Percutaneous CT-Guided biopsy is the gold standard.

Various scoring systems have been established for the diagnosis of spondylodiscitis. SponDT (Spondylodiscitis Diagnosis and Treatment) can be used to support the diagnosis of spondylodiscitis, especially in patients with back pain and elevated levels of inflammation, and can be used during the course of treatment to optimize control of therapy. Pain is rated according to MRI findings and CRP value.[7]

The novel Hamburg Spondylodiscitis Assessment Score (HSAS) is a scoring system created to identify patients at low, moderate, high and very high risk for in-hospital mortality on admission. Risk factors include diabetes, hemodialysis, intravenous drug abuse, and chronic steroid use.[8] In the differential diagnosis, inflammatory diseases of the spine such as ankylosing spondylitis, primary or metastatic tumors of the spine, degenerative diseases of the spine, radiating pain, myofascial pain syndrome, and fractures should be considered in the foreground.

In a patient with spondylodiscitis, the diagnosis can be established based on positive blood cultures (such as S. Aureus) or positive serology for brucella along with consistent clinical and radiographic findings, while biopsy is not required. Similarly, if the blood culture is positive for an invasive gram-negative enteric bacillus such as P. aeruginosa, it can be considered as the causative agent of spinal infection. Blood culture can sometimes be misleading; if there is another focus that may cause bacteremia, a needle biopsy should be performed. A second biopsy may be ordered if we are sure of the diagnosis in a patient with negative blood and needle biopsy cultures. If blood and microbiological cultures are negative and a patient cannot undergo a biopsy, the diagnosis can be made clinically and radiologically. If the initial cultures are negative, DNA-based diagnostic methods such as polymerase chain reaction (PCR) testing can be used. Clinical use of 16S ribosomal RNA (rRNA) PCR and molecular techniques such as sequencing have been found to be helpful diagnostic tools for pyogenic spondylodiscitis. If the patient has a progressive neurological deficit or if an epidural abscess is detected on imaging, an open biopsy is preferred. Apart from these cases, microorganism is attempted to be multiplied in the culture of the sample taken with CT-guided fine needle aspiration biopsy. If the

pathogenic agent cannot be identified by needle biopsy, an open biopsy should be performed. Culturing of the organism taken from the infected tissue is the most definitive test. However, it may not be possible to isolate the agent even in a biopsy taken from open infected tissue. The pathogenic agent may not be identified in 40% of patients undergoing biopsy.

Aerobic, anaerobic bacteria, tuberculosis, fungal cultures, staining with Gram and Ehrlich Ziehl Neelsen (EZN) method, pathology, and histology laboratory tests should be performed on the biopsy material.

The three distinct forms of spondylodiscitis include pyogenic spondylodiscitis, tuberculous spondylodiscitis, and brucella spondylodiscitis. Staphylococcus aureus is the most common cause of pyogenic spondylodiscitis. Other than that, gram-negative rods and streptococci can be identified. Bacterial agents trigger the immune response, while mycobacteria, fungi, and syphilis cause granulomatous inflammation. Therefore, CRP and sedimentation rate are generally higher in pyogenic spondylodiscitis. Granulomatous reaction is accompanied by caseous lesions in tuberculosis. The presence of increased alkaline phosphatase in those with normal liver and biliary tract should suggest increased bone destruction for osteomyelitis.[9] The history should first address infections that the patient has had in the last 4-6 weeks. Especially genitourinary infections should be questioned. Previous pulmonary tuberculosis or brucella infection suggests a relapse in the vertebrae. The patient's residential area and profession can give us information about the disease. Caution should be exercised in those from endemic areas of brucella and tuberculosis. Tuberculosis should be considered when miners who work in areas of coal basins present with spinal pain. Living in crowded places due to low socioeconomic status or exposure to a patient with tuberculosis should be questioned. More care should be taken in terms of brucella in individuals who are in close contact with animals (such as veterinarians, farmers, animal cutters, and laboratory workers) or those who have the opportunity to consume raw milk and dairy products and if there are recurrent fever attacks.[10]

Pyogenic spondylodiscitis is more common in obese individuals and smokers. Obesity is associated with higher rates of Staphylococcus aureus infections, especially when combined with diabetes mellitus.[11]

Anything that weakens the immune system increases the risk of infectious spondylodiscitis. For example, infective spondylodiscitis should be considered in hemodialysis patients presenting with long-term back pain with or without fever.[12] The clinical features of patients are determined by the pathogenicity of the causative microorganism and the immune response of the host.

Treatment

Identification of the microorganism causing spondylodiscitis and selection of an appropriate antimicrobial agent for the microorganism is very critical for the success of the treatment. Empirical antibiotic therapy should not be administered until a microbiological diagnosis is made, except in septic patients and patients with neurological deficits.

Choosing the right antibiotic and adequate fixation of the affected spinal segment are key concepts for treatment.[9]

A standard procedure has not been established regarding the route of administration of antibiotics, the duration of treatment, and the agents to be selected. Everyone agrees that the initial treatment should be administered by the intravenous route; however, studies on the duration of treatment are controversial. Antibiotics with high bioavailability and good bone penetration should be selected for oral therapy. The duration of antibiotic use should be long. If empirical antibiotic therapy is to be given, antibiotics that affect both gram-negative and gram-positive strains, such as vancomycin, should be selected. Vancomycin 15-20 mg/kg IV for 8-12 weeks can be used in combination with ciprofloxacin 400 mg IV for 12 weeks. Levofloxacin, ceftriaxone, or cefepime can be preferred instead of ciprofloxacin. The treatment should be in line with the culture results and test results. Antibiotic therapy for longer than 8 weeks should be administered to patients with end-stage renal disease, MRSA infection, implant material, and undrained paravertebral and psoas abscesses.[13]

Clinical improvement is checked at weeks 3-4 of empirical therapy. If there is improvement in back, waist, and neck pain and a decrease in sedimentation rate and CRP value, antibiotic therapy is continued; if there is no change, a repeat biopsy is recommended. A reduction in CRP of more than 50% at week 4 of treatment has been associated with a good prognosis.

Inappropriate use of antibiotics and short-term antibiotic use cause a relapse of the disease and prolonged length of hospital stay. Although an exact protocol cannot be established, intravenous antibiotic therapy for less than 4 weeks is not recommended because it is associated with relapses. Initial treatment is based on a combination of two bactericidal and synergistic antimicrobials at high doses. The total duration of antimicrobial therapy should be at least 12 weeks.[14] Intravenous antibiotic therapy can be used until CRP improves, and then the treatment can be switched to oral antibiotics, which will be used for 3 months. Hyperbaric oxygen therapy may be beneficial in pyogenic spondylitis. Most spinal infections can be treated medically without the requirement for surgical treatment. However, surgical treatment is required for patients who have an epidural or paravertebral abscess that affects the clinic or who have spinal

cord compression, progressive neurological deficits, significant deformity, and no significant improvement in clinical and laboratory parameters with medical treatment. Treatment aims to provide extensive neural decompression and drainage of the abscess collection. Instrumentation is preferred in cases of spinal instability. Titanium is the preferred implant material since it is very difficult for bacteria to form biofilm on titanium compared to other materials.[15] There is a significant correlation between the early detection of spondylodiscitis and successful surgical treatment.[16]

Since the diagnosis of infectious spondylodiscitis can be missed, it remains an important cause of morbidity. Therefore, it is essential that the patient be included in the rehabilitation program. First of all, appropriate nonsteroidal anti-inflammatory drugs and myorelaxants are given to reduce pain. If the pain does not relieve with these drugs, narcotic analgesics can be used. It is recommended that these patients have rest for stability and pain control. In patients with neurological deficits, the duration of rest should not exceed 3 days. Isometric exercises that will not disturb the spine stability can be given to these patients. Respiratory exercises should be part of the program in acute rehabilitation, especially in cases where the thoracic spine is affected. The corset reduces the load on the corpus by bringing the spine to hyperextension and carrying the load over the posterior elements. A corset is recommended to minimize spine movements and stabilize the spine. In infectious spondylodiscitis, vertebral collapse develops as a result of the destruction of the vertebral body, the effect of body weight, and mechanical load. Therefore, it is safer to reduce the load on the body and to perform the movement with a corset to prevent collapses. Granulomatous tissue in the affected structure is replaced by fibrosis and calcification. Over time, the fibrous tissue ossifies and osseous ankylosis develops; therefore depending on the amount of bone destruction or deformity, the corset should be used for 3 or 4 months to ensure healthy ossification. It plays a role in reducing pain and neurological deformity. If the patient has a loss of muscle strength, rehabilitation protocols are followed to strengthen muscles.

Disease Follow-up

Clinical findings, ESR, and CRP are important in follow-ups. Unimproved symptoms and no reduction in ESR by half, especially in the first 4 weeks, are associated with treatment failure. According to the IDSA 2015 guideline, it is recommended that ESR and CRP be evaluated together with clinical findings after 4 weeks of treatment. If there is improvement in clinical and laboratory parameters, a routine follow-up MRI is not recommended immediately. If there is no improvement in clinical and laboratory parameters and an abscess collection is detected at initial diagnosis, MRI may be ordered after 1 month of antimicrobial therapy.[16] Radiographs should be taken at 1 and 3 months of conservative treatment and 3 months after discontinuation of therapy to visualize the affected disc. Clinical and laboratory follow-up should be carried out throughout antimicrobial therapy and within 6 months of discontinuation of therapy.[17]

Brucellosis and Tuberculosis

In our country where brucellosis and tuberculosis are common, these two diseases should always be kept in mind in the differential diagnosis of spondylodiscitis. While tuberculosis most commonly affects the lower thoracic and lumbar regions, brucellosis mostly affects the lumbar region. In tuberculosis, intervertebral discs are preserved in the early period. Involvement of the posterior element and vertebral collapse are rare in brucellosis. Brucella usually involves a single focus, while tuberculosis more often exhibits multiple involvements. Brucella prefers the anteroinferior endplates, and the osteophyte observed in the anterior vertebral endplate is typical (anterior cupping; parrot beak sign).[18] Bone destruction is less severe compared to tuberculosis.[19]

Vertebral destruction is more severe in tuberculous spondylodiscitis. Vertebral hyperplasia is more common in brucellar spondylitis.[20] Osteophyte formation in the vertebrae is seen in almost every patient with Brucella. There is no significant disc involvement in tuberculous spondylodiscitis. Vertebral body involvement is very evident. Abscess formation is more common.[22]

Tuberculosis is difficult to grow in culture because the number of bacilli is low in extrapulmonary foci. Giant granulomas are detected in histopathology. Large paravertebral abscess formation is more common.

Brucellosis patients with low back pain and sciatic radiculopathy are often misdiagnosed as disc pathology and may even be operated. Delayed diagnosis may result in high rates of neurological sequelae in patients despite treatment. Spondylodiscitis should be considered for long-term cervical, lumbar and sacral pain in elderly patients, especially in endemic areas.[18] In order to prevent brucellosis, animals should be vaccinated, those who are in contact with animals should use personal protective equipment, and raw milk and dairy products should be avoided.[22]

Recommended regimens for the treatment of brucellosis include a combination of at least two or three antibiotics, depending on the patient's condition. Treatment should be continued for at least 3 months to prevent relapses. Patients with spinal abscesses may require surgery.

The agents frequently used for the treatment of brucellar spondylodiscitis are streptomycin, rifampicin, doxycycline,

trimethoprim/sulfamethoxazole, ciprofloxacin, and gentamicin. The American Sanford Guide recommends the use of gentamicin instead of streptomycin.[24] A triple regimen consisting of doxycycline (100 mg twice a day), rifampin (600 mg/day), and streptomycin (1 g/day IM, 21 days) is used for 3-6 months. After streptomycin treatment is discontinued at the end of three weeks, patients continue with only doxycycline and rifampin treatment. Lower recurrence rates have been reported with the combination of streptomycin and doxycycline. For patients who cannot tolerate or cannot take tetracycline such as pregnant women, trimethoprim/sulfamethoxazole therapy may be an alternative.[23]

The recommended duration of treatment for tuberculous vertebral osteomyelitis is at least 9-12 months. Twelve months of treatment should be given, especially in spinal instrumentation. Analysis of blood biochemistry should be performed to follow up the side effects of the drugs. Treatment with isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and ethambutol (ETB) is initiated in the first two months. PZA and ETB should be used for the first two months and then treatment should be continued with INH and RIF. Before initiating treatment, drug resistance should be checked.

In conclusion, infectious spondylodiscitis is a treatable disease. With culturing of the microorganism and the prompt administration of appropriate antibiotic therapy, surgical treatment is often not required. Pathogens such as tuberculosis and brucellosis are still common today. Due to the difficulties of detection and growth, they are diagnosed late, leading to irreversible complications and disability in patients. Patients who are identified early and treated aggressively continue their lives without any spinal complications. Therefore, it should be kept in mind that those presenting with spinal pain and local tenderness may also have spondylodiscitis.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

References

1. Theodore Gouliouris 1, Sani H Aliyu, Nicholas M Brown Spondylodiscitis: update on diagnosis and management J Antimicrob Chemother 2010 Nov;65 Suppl 3:iii11-24. doi: 10.1093/jac/dkq303.
2. Haidara Almansour 1, Gabriel Lennart Keller 1, Fabian Springer 1 Pyogenic Spondylodiscitis: A Pictorial Review] Rofo. 2021 Sep;193(9):993-997. doi: 10.1055/a-1447-0568. Epub 2021 Mar 27.
3. Spondilodiskitise Multidisipliner Yaklaşım Sempozyumu 29.06.2019 BEZMİ ALEM VAKIF ÜNİVERSİTESİ
4. M Titlic 1, Z Josipovic-Jelic Spondylodiscitis Bratisl Lek Listy 2008;109(8):345-7.
5. Gulay Okay 1, Yasemin Akkoyunlu 2, Sibel Bolukcu 3 Analysis of infectious spondylodiscitis: 7-years data Pak J Med Sci. 2018 Nov-Dec;34(6):1445-1451. doi: 10.12669/pjms.346.15717.
6. Knezević A et al. Clinical characteristics of infectious spondylodiscitis. Med Pregl. 2009. PMID: 20391739 English, Serbian.
7. Lars Homagk 1 2, Daniel Marmelstein 3, Nadine Homagk 3 et al. SponDT (Spondylodiscitis Diagnosis and Treatment): spondylodiscitis scoring system J Orthop Surg Res. 2019 Apr 11;14(1):100. doi: 10.1186/s13018-019-1134-9.
8. Ghada Waheed 1, Mohamed A R Soliman 2, Ahmed M Ali 2 et al. Spontaneous spondylodiscitis: review, incidence, management, and clinical outcome in 44 patients Neurosurg Focus. 2019 Jan 1;46(1):E10. doi: 10.3171/2018.10.FOCUS18463.
9. Aneta S Petkova 1 2, Christo B Zhelyazkov 1 2, Borislav D Kitov 1 2 et al. Spontaneous Spondylodiscitis - Epidemiology, Clinical Features, Diagnosis and Treatment Folia Med (Plovdiv). 2017 Sep 1;59(3):254-260. doi: 10.1515/folmed-2017-0024.
10. Omurga Enfeksiyonları 2. BASKI Editör: Prof. Dr. İ. Teoman BENLİ
11. Benjamin Schoof 1, Martin Stangenberg 2, Klaus Christian Mende 3 et al. Obesity in spontaneous spondylodiscitis: a relevant risk factor for severe disease course Sci Rep. 2020 Dec 14;10(1):21919. doi: 10.1038/s41598-020-79012-8.
12. Yueh-An Lu 1, Hsiang-Hao Hsu 1, Huang-Kai Kao 2, Chia-Hui Lee 3 et al. Infective spondylodiscitis in patients on maintenance hemodialysis: a case series Ren Fail. 2017 Nov;39(1):179-186. doi: 10.1080/0886022X.2016.1256313. Epub 2016 Nov 16.
13. Ki-Ho Park 1, Oh-Hyun Cho 2, Jung Hee Lee 3 et al. Optimal Duration of Antibiotic Therapy in Patients With Hematogenous Vertebral Osteomyelitis at Low Risk and High Risk of Recurrence Clin Infect Dis. 2016 May 15;62(10):1262-1269. doi: 10.1093/cid/ciw098. Epub 2016 Feb 24.
14. Franck Grados 1, François Xavier Lescure, Eric SennevilleJ et al. Suggestions for managing pyogenic (non-tuberculous) discitis in adults Joint Bone Spine. 2007 Mar;74(2):133-9. doi: 10.1016/j.jbspin.2006.11.002. Epub 2007 Feb 2.
15. Ahmed Hosameldin 1, Mohammed Hussein 1, Ehab Abdelhalim 2 et al. Surgical management of spontaneous thoracic and lumbar spondylodiscitis by fixation and debridement Surg Neurol Int. 2022 Feb 11;13:44. doi: 10.25259/SNI_1236_2021. eCollection 2022.
16. Berbari EF, Kanj SS, Kowalski TJ et al. Darouiche RO 2015 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults Clin Infect Dis. 2015 Sep 15;61(6):e26-46. doi: 10.1093/cid/civ482. Epub 2015 Jul 29.PMID: 26229122
17. Franck Grados 1, François Xavier Lescure, Eric Senneville et al. Suggestions for managing pyogenic (non-tuberculous)

discitis in adults Joint Bone Spine. 2007 Mar;74(2):133-9. doi:10.1016/j.jbspin.2006.11.002. Epub 2007 Feb 2.
18. Seyed Mokhtar Esmaeilnejad-Ganji 1, Seyed Mohammad Reza Esmaeilnejad-Ganji 2 Osteoarticular manifestations of human brucellosis: A review World J Orthop. 2019 Feb 18;10(2):54-62. doi: 10.5312/wjo.v10.i2.54.
19. Tao Li 1, Wei Li, Yong Du, Meng Gao et al. Discrimination of pyogenic spondylitis from brucellar spondylitis on MRI Medicine (Baltimore). 2018 Jun;97(26):e11195. doi: 10.1097/MD.0000000000011195.
20. D Ozaksoy 1, Yücesoy K, Yücesoy M et al. Brucellar spondylitis: MRI findins Eur Spine J. 2001 Dec;10(6):529-33. doi: 10.1007/s005860100285.
21. Li T, Liu T, Jiang ZS, et al. Diagnosing pyogenic, brucella and tuberculous spondylitis using histopathology and MRI: a retrospective study. Exp Ther Med. 2016 Oct;12(4):2069-2077. doi: 10.3892/etm.2016.3602. Epub 2016 Aug 22.
22. Rongjiong Zheng 1, Songsong Xie 1, Xiaobo Lu 1 et al. Systematic Review and Meta-Analysis of Epidemiology and Clinical Manifestations of Human Brucellosis in China Biomed Res Int. 2018 Apr 22;2018:5712920. doi: 10.1155/2018/5712920. eCollection 2018.
23. Gamze Kalin Unuvar 1, Aysegul Ulu Kilic 1, Mehmet Doganay 1 et al. Current therapeutic strategy in osteoarticular brucellosis North Clin Istanb. 2019 Oct 24;6(4):415-420. doi: 10.14744/nci.2019.05658. eCollection 2019.
24. https://webedition.sanfordguide.com/en
25. Georgia Vrioni 1, Adamantios Bourdakis 2, Georgios Pappas 3 et al. Administration of a triple versus a standard double antimicrobial regimen for human brucellosis more efficiently eliminates bacterial DNA load Antimicrob Agents Chemother. 2014 Dec;58(12):7541-4. doi: 10.1128/AAC.03841-14. Epub 2014 Sep 22.