North Clin Istanb 2019;6(4):415-420
doi: 10.14744/nci.2019.05658

REVIEW INFECTIOUS DISEASES & MICROBIOLOGY

Current therapeutic strategy in osteoarticular brucellosis

Gamze Kalin Unuvar, Aysegul Ulu Kilic, Mehmet Doganay

Department of Infectious Diseases, Erciyes University, Faculty of Medicine, Kayseri, Turkey

ABSTRACT

Brucellosis is a common zoonotic disease with high morbidity. In the majority of human cases, the causative agent is *B. melitensis*. Infection is transmitted to humans by direct/indirect contact with the contaminated animal products (e.g., consumption of unpasteurized milk), infectious aerosols and aborted fetus. Brucellosis often affects middle-aged adults and young people. Patients with brucellosis tend to have non-specific symptoms, including fever, chills, night sweats, joint pain and myalgia. Brucellosis affects various organs and tissues. The osteoarticular system is one of the most commonly described affected systems in humans. In several clinical studies, the prevalence of Osteoarticular Brucellosis (OB) is reported as 2-77%. Most important osteoarticular clinical forms osteomyelitis, spondylitis, sacroiliitis, arthritis and bursitis. Spondylitis and spondylodiscitis are the most frequent complications. Spondylodiscitis often affects the lumbar (especially at the L4- L5 levels) and low thoracic vertebrae than the cervical spine. Back pain and sciatica radiculopathy are the most common complaints about patients. Sacroiliitis is associated with severe pain, especially back pain in affected individuals. Spinal destructive brucellar lesions are also reported in adults in previous studies. Brucellosis is diagnosed with clinical inflammatory signs (eg. tenderness, pain) of the affected joints together with positive serological tests and positive blood/synovial fluids cultures. Serological test measures the total amount of IgM/IgG antibodies. Standard agglutination test (SAT) titer ≥1:160 is in favor of brucellosis diagnosis. Enzyme-Linked Immunosorbent Assay (ELISA) and Polymerase chain reaction (PCR) are other types of diagnostic tests. Radiological assessments, such as joint sonography, computed tomography, magnetic resonance imaging, are the most helpful radiological methods to diagnose spinal brucellosis.

The agents commonly used in the treatment of brucella spondylitis are doxycycline, streptomycin, gentamicin, ciprofloxacin, trimethoprim/sulfamethoxazole and rifampicin. The recommended regimens for treatment of brucella involve two or three antibiotics combinations. No standard treatment, physicians prescribe drugs based on conditions of the disease. Patients need a long-term (usually at three months) antibiotic therapy for mainly aiming to prevent relapses. Surgery may be required for patients with spinal abscess. This review focused on physicians' awareness for osteoarticular involvement, clinical presentation, diagnosis and current treatment of OB.

Keywords: Brucellosis; brucella spp; spondylodiscitis; sacroiliitis; standard agglutination test; treatment.

Cite this article as: *Unuvar G, Ulu Kilic A, Doganay M. Current therapeutic strategy in osteoarticular brucellosis. North Clin Istanb 2019;6(4):415-420.*

As one of the most widespread zoonoses worldwide, brucellosis is a common zoonotic disease with high morbidity. Brucellosis is an important public health problem for some countries, such as the Mediterranean Basin, Asia, Africa, South America, Eastern Europe and the Middle East. The disease called with various names, including undulant fever and Malta fever [1].

As a brucellosis zoonotic disease, brucellosis is seen common throughout the world appears to be re-emerging. Brucellosis can be seen in more than 500.000 people every year worldwide, and there are approximately 2.4 billion people at risk [2]. It is estimated that the number of patients with brucellosis may be higher than the cases reported annually. Major endemic areas include

Received: July 30, 2019 *Accepted:* August 02, 2019 *Online:* October 24, 2019

Correspondence: Dr. Gamze KALIN UNUVAR. Erciyes Universitesi Tip Fakultesi, Enfeksiyon Hastaliklari Anabilim Dali, Kayseri, Turkey.
e-mail: drgamzekln@hotmail.com

Mediterranean area, Middle East, Central Asia, China, India and sub-Saharan Africa. Brucellosis has been reported among wildlife in some regions. The prevalence of brucellosis depends upon several factors, including geography, food cooking techniques and husbandry [3].

Brucella spp is a small, nonsporulating, facultative, gram-negative coccobacilli. However, bacterial growth is slow. There is no capsules, spores or flagella in Brucella species. Several species of the pathogen are recognized within the genus, phenotypic characteristics, and prevalence of infection in different animal hosts. The most well-known species are *B. melitensis*, *B. suis*, *B. abortus* and *B. canis*. Also, human cases are commonly with *B. melitensis*. *B. melitensis* and *B. suis* are more virulent species than another *Brucella spp*. The organism is sensitive to sunlight and heat but resistant to drying and freezing and can survive for two months in cheese made of from milk from a goat or sheep. The various species of genus brucella have different host preferences. Main animal reservoirs for *B. melitensis* are sheep, goats and camels. The main reservoir for *B. abortus* is cows, for *B. suis* is swine, for *B. canis* is dogs. *B. Neotoma* (desert woodrats) and *B. ovis* (sheep) are non-pathogenic for humans [4, 1].

The common route for transmission of the disease is direct/indirect contact with contaminated animal products (e.g., unpasteurized milk, undercooked raw meat and unpasteurized cheese). Direct contact through the skin lesions or conjunctiva with infectious tissues and infectious aerosols are the other important ways of transmission to humans. The aborted fetus, placenta and uterine discharges of animals are highly infectious for humans. Family history of the disease is very common in endemic areas. Screening household members of an index case allows early diagnosis and consequently prevent the complications. Human-to-human transmission is unusual. Rare cases through vertical route (congenital brucellosis) have been reported. Tissue transplantation, blood transfusion and sexual contact may also occur, but very uncommon. Laboratory workers are at a high risk of acquiring brucellosis due to inadequate laboratory precautions. Biosafety level-3 practices are recommended for all manipulations of *Brucella spp*. cultures and laboratory workers should be informed about precautions [5, 6].

Brucellosis often affects middle-aged adults and young people. The results of some studies showed that male and female individuals are affected equally in brucellosis, while there are also some studies which reported that brucellosis is more prevalent in male may be due to their jobs (e.g., animal husbandry) in endemic regions [7, 8].

The incubation period of brucellosis is usually 1-4 weeks; but in some cases, it may be several months. This infection has a broad clinical spectrum like asymptomatic or severe/fatal disease. Patient's manifests are non-specific symptoms, such as fever, chills, night sweats, joint pain and myalgia. The fever may be high or slightly elevated and usually lasts for days to weeks. Brucellosis may present as a fever of unknown origin. Hepatomegaly, splenomegaly, or lymphadenopathy may be observed. None of them are characteristic of brucellosis that affects various organs and tissues. Relapse usually occurs in 5–30% of the patients, within the first six months following completion of treatment. Inappropriate choice of antibiotics and a shorter duration of treatment are associated with relapsing cases [9]. Tuberculosis, infectious mononucleosis, collagen vascular diseases, autoimmune diseases and malignancy should all be considered in the differential diagnosis of brucellosis.

The severity of complications or response to treatment of brucellosis is more benign in children than adults. Also, during pregnancy, brucellosis may bring about spontaneous abortions, intrauterine infection with fetal death [10, 11].

Education is an important strategy for prevention of brucellosis. The prevention of brucellosis must cover the characteristics of microbial agents, clinical presentation, diagnosis and treatment, prophylaxis of the disease and protection measures. Recent studies have shown that vaccination in healthy animals is a highly effective strategy for protection. However, to our knowledge, there is no licensed vaccine for humans. Also, for the use of prophylaxis after animal and laboratory exposures, there is supportive experimental evidence. The most recommended combination is 600 mg rifampicin, plus 200 mg doxycycline daily [12].

The most common complication of brucellosis is osteoarticular involvement. In several clinical studies, the prevalence of osteoarticular brucellosis is reported as 2-77%. Osteoarticular brucellosis may be seen in acute or chronic clinic features. Important osteoarticular clinical applications are spondylitis, sacroiliitis, osteomyelitis, bursitis and peripheral arthritis. Presence of nonspecific symptoms and variable clinical feature often cause a delay in diagnosis of the diseases [13, 14].

Osteoarticular Brucellosis Clinical Forms

Sacroiliitis

The sacroiliac joint is the most common region of musculoskeletal involvement of osteoarticular brucellosis. The incidence of sacroiliitis is approximately 2-45% [13]. Arthritis and sacroiliitis are usual presentations of an acute form. Also, severe back pain in the affected region of sacroiliitis is the most common symptom. Fever, sweating, joint swelling, redness around the skin of a joint and malaise are less common symptoms. Sacroiliitis can be unilateral or bilateral forms and is rarely reported with iliac muscle abscess [13, 15, 16].

Spondylodiscitis, Spondylitis

The prevalence rate of spondylitis is approximately 2-60% [14] and more prevalent in older patients and patients with prolonged illness before the treatment. The involvement of brucellosis firstly begins at the discovertebral junction, after it may spread to other vertebral parts. The lumbar vertebrae are involved more frequently (%60) than the thoracic (19%) and cervical vertebrae (12%) [14, 16, 17].

Spondylodiscitis is an inflammation of vertebra and discs. This form of osteoarticular involvement of brucellosis occurs through the hematogenous spread and neurological sequels cause after an inappropriate treatment. Spondylodiscitis more commonly affects the lumbar (especially at the L4- L5 levels) and low thoracic vertebrae than the cervical spine. Back pain and sciatica radiculopathy are the most common complaints for patients. Paresthesia or reflex changes may occur due to cord and neural compression. In physical examination, Laseque test is a positive finding. Spinal destructive brucellar lesions have also been reported in adults in previous studies. In brucella induced spondylitis, psoas abscess, paravertebral abscess, or epidural abscess may occur [13, 17, 18].

Peripheral Arthritis

The prevalence of brucellosis-induced peripheral arthritis is less (14-26%) compared with vertebral features. The most frequently involved large joints are knees, hip and ankle. Clinical presentations and physical examinations are nonspecific. Arthritis may occur in patients with acute, subacute, or chronic brucellosis. Peripheral arthritis may involve joints septic and reactive mechanisms associated with pathogens. Septic arthritis is the rare complication of brucellosis that progresses slowly and may cause capsular erosions. The most useful diagnostic methods are the assessment of synovial fluid and blood cultures. Especially, brucella-induced hip arthritis is more complicated than others. The serious complication may be an important problem due to the delay in treatment [19, 20].

Brucellar osteomyelitis is another manifestation of the disease. Osteomyelitis may result in a pathologic fracture or prosthetic extraarticular equipment. During brucella bacteremia, the prosthetic joint can be involved, and arthroplasty may be useful for treatment [21]. Tenosynovitis and bursitis have also been reported in the literature [22].

Diagnosis of Osteoarticular Brucellosis

There are several diagnostic methods for brucellosis. Osteoarticular brucellosis is diagnosed with clinical inflammatory signs (e.g., tenderness, pain) of the affected joints together with positive serological tests and/or positive culture of blood/synovial fluids cultures. Inappropriate diagnosis and treatment of the disease may result in high morbidity in patients. Brucellosis is most commonly diagnosed by serological methods, such as standard tube agglutination (STA) and enzyme-linked immunosorbent assay (ELISA). STA (Wright) measures the total amount of immunoglobulin M (IgM)/immunoglobulin G (Ig G) antibodies. Immunoglobulin M antibody firstly appears than Ig G antibody. All these antibodies are active in agglutination tests [23]. Standard agglutination (Wright) measures total Ig M and G, while the ME-2 test only measures Ig G antibody. ME-2 test is a good marker to follow the activity of disease after initiation of therapy. STA titer ≥1:160 and ME-2 test titer is ≥1:80 in favor of brucellosis diagnosis [12]. Negative agglutination titers do not exclude brucella infection, and it can be observed during disease. STA is negative during the early phase of the disease and in the presence of blocking antibodies. Coombs test (antihuman globulin test), which is essential for complicated and chronic cases, eliminates the effects of blocking antibodies [23, 24].

Brucellacapt is an immunocapture-agglutination technique, which detects all immunoglobulins against Brucella. Brucellacapt test could help to detect the disease in patients with long evolution times, which cannot be detected with the SAT. Some studies reported that both of Brucella Capt and Coombs tests show higher titers of ≥1/160 for acute brucellosis. However, when titers less than 1/320 were used for diagnosis, test specificity may

be decreased. These tests may persist positive for a long time after therapy in cured patients. After a successful treatment, a decrease in specific antibody titers is more rapid in Brucellacapt than the other tests [25, 26].

Polymerase chain reaction (PCR) that is a useful molecular test has high sensitivity. PCR has enormous potential to detect bacteremia for relapsing cases and the exclusion of chronic brucellosis [27, 28].

The gold standard for diagnosis is blood culture or tissues (e.g., synovial fluid, bone marrow) culture; however, isolation of the microorganism is quite difficult, bone marrow aspirate culture is invasive and clinically non-practical [27]. Blood cultures sensitivity ranges are around 17% to 85%. Some studies reported that the growth time of brucella bacteria in blood culture was significantly shorter in cases with osteoarticular brucellosis [29]. Especially, the culture method is suggested to the patients who have a high bacterial load [29, 30]. The synovial fluid analysis may help to separate Brucella arthritis from other causes of arthritis. The white blood cell count can be measured around 15.000 cells/microL. In the synovial fluid, while in brucella arthritis lymphocytes frequently predominate, whereas polymorphonuclear leukocytes frequently predominant in septic arthritis due to other bacteria [27].

Leukocyte count, C- reactive protein (CRP) and erythrocyte rate (ESR) that are additional diagnostic methods may be beneficial to follow up the treatment response. High CRP and leukocyte levels are associated with an inflammatory condition. Some studies have investigated the higher NLR (neutrophil/lymphocyte ratio), MLR (monocyte/lymphocyte ratio) and ESR, CRP levels could be effective indicators for the diagnosis of osteoarticular brucellosis. The NLR and MLR are easier tests compared with the other inflammation markers like CRP and ESR [31].

Radiological assessments, such as joint sonography, computed tomography (CT) and magnetic resonance imaging (MRI), are helpful to diagnose spinal brucellosis. They can determine the affected sites. In the acute phase of diseases, X-rays may reveal the involvement of multiple vertebral bodies and joint lesions. The characteristic features of the disease, such as vertebrae destruction and vertebrae sclerosis, can be determined precisely on the CT scan. MRI is very sensitive to changes like the destruction of vertebral body bone, the intervertebral discs, and abscesses within and outside the vertebral canal [12].

In early-stage of disease, MRI sensitivity detects the change in vertebral bodies and surrounding soft tissue. Spinal brucellosis often involves the endplates of the junctions between the vertebral bodies and the intervertebral discs. Especially for the diagnosis of spinal nerves compression, MRI is a more effective method than the others [32].

Treatment

Controlling the illness effectively, preventing transmission and preventing complications are important for the treatment of brucellosis. The aims of antimicrobial therapy are to treat acute infection, relieve symptoms and prevent relapse. The agents often used in the treatment of brucellar spondylitis are streptomycin, rifampicin, doxycycline, trimethoprim/sulfamethoxazole, ciprofloxacin and gentamicin [33]. The recommended regimens for the treatment of disease involve two or three antibiotic combinations. Physicians prescribe drugs, depending on whether the disease is complex or not because there is no standard combination for osteoarticular involvement. Selection of an appropriate antibiotic combination should be made on the basis of the patient. The triple regimen that the World Health Organization (WHO) have recommended, doxycycline (100 mg twice a day) plus rifampin (600 mg/day) plus streptomycin (1 g/day IM, 21 days) over six months is more effective for the treatment [34, 35]. At the end of three weeks, after discontinuing streptomycin treatment, patients are treated only with doxycycline plus rifampin therapy.

The most frequently used combinations include streptomycin, which has favorable results for osteoarticular brucellosis in previous studies. On the other hand, lower relapse rates were reported with a combination of streptomycin and doxycycline [36].

Optimal duration of therapy is about 3-6 months for osteoarticular involvement; it can be beneficial to cure. Streptomycin or gentamicin has been used for three weeks. Doxycycline and rifampin combination therapy is found to be associated with relapses [35, 37]. Long-term (usually at three months) antibiotic therapy can be effective to prevent relapses in patients [37, 38] because a prolonged course of treatment is important, especially in case of the absence of radiological improvement to prevent possible sequelae [38]. For patients who do not tolerate or not receive tetracycline (e.g., pregnancy), trimethoprim/sulfamethoxazole therapy could be an alternative [39].

To our knowledge, there is no specific evidence for prophylaxis after exposure to *Brucella spp*. However, some studies recommend after low-risk exposure rifampin plus doxycycline therapy for three weeks and after a major exposure to aerosol for six weeks [40].

In the case of continuing systemic signs despite adequate antimicrobial therapy, surgical interventions can be proposed. Furthermore, surgery may be required for a specific group of patients with particularly spinal abscess, vertebral collapse, bone destruction and cord compression [12].

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Adetunji SA, Ramirez G, Foster MJ, Arenas-Gamboa AM. A systematic review and meta-analysis of the prevalence of osteoarticular brucellosis. PLoS Negl Trop Dis 2019;13:e0007112.
2. Franc KA, Krecek RC, Häsler BN, Arenas-Gamboa AM. Brucellosis remains a neglected disease in the developing world: a call for interdisciplinary action. BMC Public Health 2018;18:125.
3. Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. Lancet Infect Dis 2006;6:91–9.
4. Pappas G, Akritidis N, Bosilkovski M, Tsianos E. Brucellosis. N Engl J Med 2005;352:2325–36.
5. Young EJ. Brucella species. In: Mandell GL, Bennet JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 6th ed. Philadelphia. USA: Elsevier Churchill Livingstone; 2005. p. 2669–74.
6. Doganay M, Mese Alp E. Bruselloz. In: Willke Topcu A, Soyletir G, Doganay M, editors. Enfeksiyon Hastalıkları ve Mikrobiyolojisi. 3rd ed. Istanbul: Nobel Tıp Kitabevleri; 2008. p. 897–909.
7. Arévalo Lorido JC, Carretero Gómez J, Romero Requena J, Bureo Dacal JC, Vera Tomé A, Bureo Dacal P. Brucellar spondylitis and meningoencephalitis: a case report. Neth J Med 2001;59:158–60.
8. Turan H, Serefhanoglu K, Karadeli E, Togan T, Arslan H. Osteoarticular involvement among 202 brucellosis cases identified in Central Anatolia region of Turkey. Intern Med. 2011;50:421–8.
9. Ulu-Kilic A, Metan G, Alp E. Clinical presentations and diagnosis of brucellosis. Recent Pat Antiinfect Drug Discov 2013;8:34–41.
10. Doganay M, Aygen B. Human brucellosis: An overview. Int J Infect Dis 2003;7:173–82.
11. Khan MY, Mah MW, Memish ZA. Brucellosis in pregnant women. Clin Infect Dis 2001;32:1172–7.
12. Bao Y, Tian M, Li P, Liu J, Ding C, Yu S. Characterization of Brucella abortus mutant strain Δ22915, a potential vaccinecandidate. Vet Res 2017;48:17.
13. Esmaeilnejad-Ganji SM, Esmaeilnejad-Ganji SMR. Osteoarticular manifestations of human brucellosis: A review. World J Orthop 2019;10:54–62.
14. Hashemi SH, Keramat F, Ranjbar M, Mamani M, Farzam A, Jamal-Omidi S. Osteoarticular complications of brucellosis in Hamedan, an endemic area in the westof Iran. Int J Infect Dis 2007;11:496–500.
15. Batmaz I, Tekin R, Sariyildiz MA, Deveci O, Cevik R. A Case of Brucellosis With Simultaneous Dactylitis and Sacroiliitis. Journal of Medical Cases 2012;3:304–7.
16. Skalsky K, Yahav D, Bishara J, Pitlik S, Leibovici L, Paul M. Treatment of human brucellosis: systematic review and meta-analysis of randomised controlled trials. BMJ 2008;336:701–4.
17. Erdem H, Elaldi N, Batirel A, Aliyu S, Sengoz G, Pehlivanoglu F, et al. Comparison of brucellar and tuberculous spondylodiscitis patients: results of the multicenter "Backbone-1 Study". Spine J 2015;15:2509–17.
18. Mantur BG, Amarnath SK, Shinde RS. Review of clinical and laboratory features of human brucellosis. Indian J Med Microbiol 2007;25:188–202.
19. Chin YT, Krishnan M, Burns P, Qamruddin A, Hasan R, Dodgson AR. Brucella melitensis sternal osteomyelitis following median sternotomy. J Infect Chemother 2014;20:574–6.
20. Ebrahimpour S, Bayani M, Moulana Z, Hasanjani Roushan MR. Skeletal complications of brucellosis: A study of 464 cases in Babol, Iran. Caspian J Intern Med 2017;8:44–8.
21. Oner M, Guney A, Halıcı M, Kafadar I. Septic Loosening Due to Brucella Melitensis After Bilateral Knee Prosthesis and Two-Stage Total Knee Prosthesis Revision. Erciyes Med J 2012;34:97–9.
22. Tekin R, Ceylan Tekin F, Ceylan Tekin R, Cevik R. Brucellosis as a primary cause of tenosynovitis of the extensor muscle of the arm. Infez Med 2015;23:257–60.
23. Mantur BG, Biradar MS, Bidri RC, Mulimani MS, Veerappa, Kariholu P, et al. Protean clinical manifestations and diagnostic challenges of human brucellosis in adults: 16 years' experience in an endemic area. J Med Microbiol 2006;55:897–903.
24. Bosilkovski M, Katerina S, Zaklina S, Ivan V. The role of Brucellacapt test for follow-up patients with brucellosis. Comp Immunol Microbiol Infect Dis 2010;33:435–42.
25. Orduña A, Almaraz A, Prado A, Gutierrez MP, Garcia-Pascual A, Dueñas A, et al. Evaluation of an immunocapture-agglutination test (Brucellacapt) for serodiagnosis of human brucellosis. J Clin Microbiol 2000;38:4000–5.
26. Casao MA, Navarro E, Solera J. Evaluation of Brucellacapt for the diagnosis of human brucellosis. J Infect 2004;49:102–8.
27. Memish ZA, Almuneef M, Mah MW, Qassem LA, Osoba AO. Comparison of the Brucella Standard Agglutination Test with the ELISA IgG and IgM in patients with Brucella bacteremia. Diagn Microbiol Infect Dis 2002;44:129–32.
28. Baldi PC, Giambartolomei GH, Wallach JC, Velikovsky CA, Fossati CA. Limited diagnostic usefulness of antibodies to cytoplasmic proteins of Brucella in early-treated human brucellosis. Scand J Infect Dis 2001;33:200–5.
29. Mantur BG, Amarnath SK, Shinde RS. Review of clinical and laboratory features of human brucellosis. Indian J Med Microbiol 2007;25:188–202.
30. Mantur BG, Mangalgi SS. Evaluation of conventional castaneda and lysis centrifugation blood culture techniques for diagnosis of human brucellosis. J Clin Microbiol 2004;42:4327–8.
31. Balın ŞÖ, Tartar AS, Akbulut A. The predictive role of haematological parameters in the diagnosis of osteoarticular brucellosis. Afr Health Sci 2018;18:988–94.
32. Ozaksoy D, Yücesoy K, Yücesoy M, Kovanlikaya I, Yüce A, Naderi S. Brucellar spondylitis: MRI findings. Eur Spine J 2001;10:529–33.
33. Solera J, Martínez-Alfaro E, Espinosa A. Recognition and optimum

treatment of brucellosis. Drugs 1997;53:245–56.
34. WHO. Brucellosis in humans and animals Geneva: World Health Organization, 2006. Available at: https://apps.who.int/iris/handle/10665/43597. Accessed Sep 27, 2019.
35. Pappas G, Papadimitriou P, Christou L, Akritidis N. Future trends in human brucellosis treatment. Expert Opin Investig Drugs 2006;15:1141–9.
36. Ulu-Kilic A, Karakas A, Erdem H, Turker T, Inal AS, Ak O, et al. Update on treatment options for spinal brucellosis. Clin Microbiol Infect 2014;20:O75–82.
37. Alp E, Koc RK, Durak AC, Yildiz O, Aygen B, Sumerkan B, et al. Doxycycline plus streptomycin versus ciprofloxacin plus rifampicin in spinalbrucellosis [ISRCTN31053647]. BMC Infect Dis 2006;6:72.
38. Ulu-Kilic A, Sayar MS, Tütüncü E, Sezen F, Sencan I. Complicated brucellar spondylodiscitis: experience from an endemic area. Rheumatol Int 2013;33:2909–12.
39. Zheng R, Xie S, Lu X, Sun L, Zhou Y, Zhang Y, et al. A Systematic Review and Meta-Analysis of Epidemiology and Clinical Manifestations of Human Brucellosis in China. Biomed Res Int 2018;2018:5712920.
40. Pappas G, Seitaridis S, Akritidis N, Tsianos E. Treatment of brucella spondylitis: lessons from an impossible meta-analysis and initial report of efficacy of a fluoroquinolone-containing regimen. Int J Antimicrob Agents 2004;24:502–7.