Treatment of Pediatric Brucellosis

Pediatrik Bruselloz Tedavisi

Aylin DİZİ IŞIK[a],
Gülşen AKKOÇ[a],
Eda KEPENEKLİ KADAYIFÇI[a]

[a]Marmara University Faculty of Medicine, Division of Pediatric Infectious Diseases, İstanbul, Türkiye

Yazışma Adresi/*Correspondence:*
Eda KEPENEKLİ KADAYIFÇI
Marmara University Faculty of Medicine, Division of Pediatric Infectious Diseases, İstanbul, Türkiye
ekepenekli@yahoo.com

ABSTRACT Brucellosis is one of the most common zoonotic infections worldwide and represents a significant public health problem throughout the world, especially in resource-limited countries. It is primarily transmitted to humans by the consumption of contaminated food, such as unpasteurized dairy products, of infected animals (cattle, sheep, goats, camels, pigs, or other animals) or by direct contact with their tissues or fluids. Brucellosis presents with acute or insidious onset, featuring symptoms such as fever, weakness, headache, weight loss, night sweats, and arthralgia. Physical examination findings are non-specific and various. Hepatomegaly, splenomegaly, and/or lymphadenopathy may be observed. Patients with these symptoms and findings in endemic regions should be evaluated for brucellosis. Diagnosis is confirmed by bacteriological or serological tests. The treatment is based on the prolonged and combined use of antibiotics with intracellular action. Brucellosis may proceed with relapse, complications, sequelae, and even potential mortality if therapy is not given promptly and completely.

Keywords: *Brucella*; zoonotic infection; pediatric; treatment

ÖZET Bruselloz, dünya çapında en yaygın görülen zoonotik enfeksiyonlardan biridir ve özellikle gelişmekte olan ülkelerde önemli bir halk sağlığı sorunudur. İnsanlara çoğunlukla enfekte hayvanlardan (sığır, koyun, keçi, deve, domuz vd.) elde edilen yiyeceklerin (pastörize edilmemiş süt ürünleri gibi) tüketilmesi ve bu hayvanların doku veya sıvılarına temas yoluyla bulaşır. Bruselloz akut ya da sinsi başlangıçlı ateş, halsizlik, baş ağrısı, kilo kaybı, gece terlemeleri ve artralji ile kendini gösterir. Fizik muayene bulguları spesifik olmamakla birlikte değişkendir: Hepatomegali, splenomegali ve lenfadenopati görülebilir. Bruselloz, endemik bölgelerde yaşayanlarda bu semptom ve bulgular geliştiğinde ayırıcı tanılar arasında yer almalıdır. Tanı, bakteriyolojik veya serolojik testlerle doğrulanır. Tedavide hücre içi aktivite gösteren antibiyotiklerin kombine ve uzun süreli kullanımı temel ilkedir. Bruselloz tedavisi, zamanında ve tam olarak yapılamadığında relaps, komplikasyon ve sekeller ile seyredebilir ve mortalite ile sonuçlanabilir.

Anahtar Kelimeler: *Brusella*; zoonotik enfeksiyon; pediatrik; tedavi

Brucellosis, also known as “undulant fever”, “Mediterranean fever” or “Malta fever”, is a zoonotic infection transmitted to humans by the consumption of food products (such as unpasteurized dairy products) or contact with tissue or fluids of infected animals (cattle, sheep, goats, camels, pigs, or other animals). It is the most common zoonosis worldwide and an important public health problem throughout the world, especially in many resource-limited countries.[1,2]

EPIDEMIOLOGY

Brucellosis is still one of the most common zoonotic infections worldwide and is endemic in many regions of the world, especially more prevalent in the Mediterranean countries of Europe, North and East Africa, the Middle East, South, and Central Asia,

TO CITE THIS ARTICLE:
Dizi Işık A, Akkoç G, Kepenekli Kadayıfçı E. Treatment of pediatric brucellosis. Öncel S, ed. Antibiotic Selection in Childhood Infections. 1st ed. Ankara: Türkiye Klinikleri; 2024. p.43-51.

and Central and South America. It is estimated that approximately 3.5 billion people in the world carry the permanent risk of acquiring brucellosis. Although accurate estimates of the prevalence of disease are lacking due to underreporting and underdiagnosis, the incidence varies between 0.03-106/100,000 and more than 500,000 new cases are reported annually.[1,3,4] Childhood brucellosis accounts for 10-30% of cases.[5] All age groups and both genders are susceptible to the infection, however, children older than five years are more frequently vulnerable because they are more involved in animal care. Turkey is one of the endemic regions for brucellosis, which is more prevalent in Eastern and Southeastern Anatolian Regions. According to national statistical data in 2017, 6,457 cases were reported.[6,7]

MICROBIOLOGY AND TRANSMISSION

Brucella bacteria are small, gram-negative, non-capsulated, non-motile, non-spore-forming, and facultative intracellular coccobacilli. There are four different *Brucella* species, that mostly affect humans, including *B. melitensis* (goats and sheep), *B. abortus* (cattle), *B. suis* (swine), and *B. canis* (dogs). The most common cause of human brucellosis is *B. melitensis*. *B. suis* and *B. melitensis* infections in humans are typically more virulent than *B. abortus* or *B. canis* infections. Additionally, infrequent marine strains of the human pathogens *B. pinipedialis* and *B. ceti* were identified in animals.[1,8] *Brucella* organisms can remain alive for up to two days at 8ºC in unpasteurized milk, three weeks in frozen meat, and three months in unpasteurized goat's milk cheese. Organisms excreted through animal feces can survive for more than 40 days in moist soil. These organisms are vulnerable to heat, radiation, disinfectants, and pasteurization.[9]

Brucellosis can be transmitted to humans through the consumption of unpasteurized dairy products of infected animals, contact of skin or mucous membranes with infected animal tissue (such as placenta) or fluids (such as blood, urine, or milk), and inhalation of infected aerosol droplets. Consumption of unpasteurized dairy products (especially raw milk, fresh cheese, butter, and ice cream) is the most common route of transmission. Hard cheese, yoghurt, and sour milk are less contagious because of undergoing the fermentation process. Additionally, brucellosis is a common occupationally-related hazard for veterinarians, slaughterhouse workers, meat packers, and laboratory workers. Blood transfusion, tissue transplantation, transplacental, breastfeeding, and sexual transmission are extremely rare.[1,5,10] *Brucella* has been reported as a possible type B biological weapon by the Centers for Disease Control and Prevention (CDC).[11]

CLINICAL MANIFESTATIONS

The clinical manifestations of childhood brucellosis are quite variable, due in part to the variable epidemiological characteristics and pathogenicity of different strains (Table 1). A systemic illness characterized by nonspecific complaints with a paucity of abnormal physical findings can have an acute or insidious onset. The incubation period of brucellosis is normally 1-3 weeks, but it can take several months before presenting signs of infection. Manifestations include undulant fever in which the temperature can vary from 37°C in the morning to 40ºC in the afternoon, night sweats with a peculiar odor, weakness, malaise, anorexia, weight loss, arthralgia, myalgia, back pain, abdominal pain, and headache. Fever, arthralgia, night sweats, and peripheral arthritis are the most common presenting symptoms and signs. Other common physical findings may include lymphadenopathy and hepatosplenomegaly.[1,4,5,10] Osteoarticular involvement is the most common localized form of brucellosis in children. Joint involvement is usually monoarthritis rather than polyarthritis. Monoarthritis is more common than polyarthritis. The most commonly affected joints are the hips, knees, ankles, and sacroiliac joints respectively.[5] Spondylitis, osteomyelitis, and inflammatory arthropathy have also been rarely described in childhood, contrary to adults. Spondylitis is a serious complication of brucellosis and is more common in late-diagnosed patients. Spondylitis often has sequelae following treatment.[12,13] Although osteoarticular involvement is more common, there are other less frequent clinical presentations. Neurobrucellosis may be rarely seen in children. Acute meningitis and meningoencephalitis are prominent manifestations of most of the affected children. Depression, inattention, myelitis, radiculoneuritis, and brain abscess also have been seen in children with brucellosis as case reports.[14,15] Gastrointestinal involvement other than the reticuloendothelial system is rare; reported as hepatic or splenic abscess, cholecystitis, pancreatitis, ileitis, colitis, and peritonitis.[8] Genitourinary involvement is another common complication of brucellosis, especially in adults. Pediatric cases of brucellosis rarely exhibit epidydimo-orchitis which is frequently found in adults.[16,17] Rare cases of interstitial nephritis, membranous nephropathy, and glomerulonephritis have also been reported.[18] Pulmonary involvement has been reported in about 2% of the cases and presents as hilar adenopathy, lobar pneumonia, lung nodules, pleural effusion, and thoracic empyema.[19] Cardiovascular manifestations of brucellosis include endocarditis, myocarditis, pericarditis, as well as aneurysms affecting the aorta and cerebral blood vessels. Failure to

promptly diagnose the condition can lead to severe and life-threatening complications. Endocarditis is a common cardiovascular complication and is the main cause of death associated with brucellosis.[20,21] Ocular involvement is rare and most commonly seen as uveitis. Other manifestations include keratoconjunctivitis, corneal ulcers, iridocyclitis, keratitis, choroiditis, optic neuritis, papilledema, and endophthalmitis.[22] Cutaneous findings manifest as macular, maculopapular, scarlatiniform, papulonodular, and erythema nodosum-like rashes, ulcerations, petechiae, purpura, granulomatous vasculitis and abscesses.[23] Hematologic abnormalities, such as anemia, leukopenia, and thrombocytopenia, are frequently observed during the course of brucellosis. These alterations are usually mild and can be promptly resolved with appropriate antimicrobial treatment. In some cases, thrombocytopenia may become severe, leading to bleeding in the skin and mucosal areas. The reasons behind this complication are likely multifactorial, involving factors such as hypersplenism, disseminated intravascular coagulation, bone marrow suppression, hemophagocytosis, and immune mechanisms.[24,25]

Indeed, neonatal brucellosis is a rare occurrence, but it can happen through various routes of transmission. The infection may be transmitted to the fetus through the placenta during a maternal bacteremic phase, or the neonate may acquire the infection during birth from exposure to the mother's blood, urine, or vaginal secretions. Additionally, breastfeeding can also be a mode of transmission in the setting where the mother is infected. *B. melitensis* is the most commonly documented causative agent in neonatal brucellosis cases. However, there have been reports of cases caused by *B. abortus* as well.[26,27]

Chronic brucellosis is a clinical condition that is still not fully understood and is subject to ongoing debate. Although there is no widely accepted definition for this issue, many experts agree that the term "chronic brucellosis" should be applied to patients whose clinical symptoms persist for 12 months or longer since the initial diagnosis, the lack of a clear-cut standard contributes to the ongoing debate. Patients can be categorized into three courses based on this criterion: (i) Relapse, (ii) chronic localized infection, and (iii) delayed convalescence (Table 1) (1). Relapse is defined as the reappearance of characteristic signs and symptoms, with or without a positive culture, after the completion of a previous course of treatment. Patients experiencing a relapse is typically present objective signs of infection, such as fever, along with persistently elevated levels of IgG antibodies in their serum. It is important to note that most relapses occur within six months after the discontinuing therapy.[1,28] Chronic localized infection is defined as the recurrence of characteristic signs and symptoms, with or without a positive blood culture. This is likely due to the failure to eliminate infections that are inaccessible to antibiotics, such as osteomyelitis or deep tissue infection. These patients exhibit objective signs of infection such as fever, although over extended periods symptoms may appear intermittently over extended periods, followed by symptom-free periods. Chronic localized infections are characterized by persistently elevated levels of IgG antibodies in their serum similar to patients experiencing relapse.[1,29] Delayed convalescence refers to the condition in which patients continue to experience symptoms, even after completing a course of therapy, and without showing objective signs of infection, such as fever. Additionally, in these patients, titers of antibodies may have declined or even disappeared. The specific cause of delayed convalescence is not well understood. Some psychological studies suggest that there may be a higher incidence of personality disorders among these patients, which may have been present before the onset of brucellosis.[1,30]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

In children living in endemic areas with clinical findings, a history of exposure, and/or a family history of brucellosis, brucellosis should be suspected. If brucellosis is suspected, blood and other specimen cultures and serology tests should be performed in the setting of suspected brucellosis.[10] The gold standard for definitive diagnosis gold standard is the isolation of *Brucella* organisms from blood, body fluids (such as urine, CSF, synovial fluid, and pleural fluid), or tissue samples (such as bone marrow, lymph nodes, or liver biopsy). Additionally, evidence of a fourfold or greater increase in *Brucella* antibody titer between acute and convalescent-phase serum specimens obtained greater than or equal to 2 weeks apart is also recognized as definitive diagnosis by the CDC. The sensitivity of blood culture for diagnosing brucellosis ranges from 15% to 70% in acutely infected patients otherwise even lower in chronically infected patients. Bone marrow culture is reported to be more sensitive than blood culture in detecting the causative agent. Therefore, bone marrow culture is considered as gold standard specimen for the diagnosis. The laboratory must be notified of any suspicion of brucellosis so that appropriate measures can be taken to ensure proper handling of samples and adequate maintenance of cultures. This is because Brucella spp. grow slowly and can be used as biological weapons.[2,4,31] In cases where bacteriologic

confirmation is not available, a presumptive diagnosis can be made if the Brucella total antibody titer is greater than or equal to 1:160 by standard tube agglutination test (SAT) or Brucella microagglutination test (BMAT) in one or more serum specimens obtained after the onset of symptoms or detection of Brucella DNA is detected in a clinical specimen by PCR assay.[2,31]

Brucellosis diagnosis is achieved through various serological methods that detect antibodies against lipopolysaccharides or other antigens. The most common tests are the SAT and enzyme-linked immunosorbent assay (ELISA) tests. Additional screening tests include the Rose Bengal agglutination test and immunochromatographic agglutination test. Combining two serological tests may increase the likelihood of diagnosis. In endemic areas, values greater than 1:160 and in other regions, values greater than 1:320 are considered positive. The test exhibits high sensitivity and specificity, with rates of 95% and 100%, respectively. The SAT is a widely used test for detecting B. canis infection. ELISA tests measure the levels of IgM, IgG, and IgA antibodies developed against bacterial antigens. However, the sensitivity of ELISA for IgM and IgG is lower than that of the SAT, with rates of 79% and 45.6%, respectively. However, when IgM and IgG ELISA are used in combination, their sensitivity and specificity are comparable to that of SAT (94.1% and 97.1%, respectively).[32] SAT measures the total amount of agglutinating antibodies of both IgM and IgG, while the 2-mercaptoethanol (2-ME) test specifically measures IgG antibodies. The 2-ME test is particularly useful in indicating active infection. When evaluating suspected cases of brucellosis, it may be more valuable to use a combination of the SAT and 2-ME tests. A patient with compatible clinical symptoms and signs of brucellosis and an SAT titer of 1:320 or higher, along with a 2-ME test titer of 1:80 or higher, is a good predictor of the disease's existence. This combination of test results helps differentiate between acute and chronic brucellosis. Elevated IgG titers in the SAT typically indicate an acute form of the disease and suggest an ongoing infection. Conversely, a negative 2-ME test result after completion of therapy indicates a favorable response to treatment.[5] For rapid results, the Rose Bengal agglutination test (with a sensitivity of 87% and specificity of 100%) can be used as a screening test.[33] However, serological tests, as mentioned above, have disadvantages, such as false positive and false negative results. Cross-reactions may occur in the SAT with other bacteria, such as *Francisella tularensis, Yersinia enterocolitica, Escherichia coli, Salmonella urbana,* and *Vibrio cholerae*. False-negative results are common in the early stages of infection, immunosuppressed conditions, and in the presence of deficient or blocking antibodies (serum agglutination). In the SAT, a 'prozone' phenomenon may occur, which inhibits agglutination at low dilutions due to excessive antibodies or nonspecific serum factors.[8] Routine laboratory tests, including complete blood count and liver function tests, can be useful in detecting hematological abnormalities such as anemia, leukopenia, or relative lymphocytosis with leukocytosis, thrombocytopenia, and elevated transaminase levels that may suggest brucellosis.[8,34] In brucellosis arthritis, synovial fluid typically shows a high white blood cell count (predominantly lymphocytes) of around 15,000 cells/microliter. The organism can be demonstrated in synovial fluid culture. In cases of neurological involvement in brucellosis, cerebrospinal fluid findings may reveal pleocytosis (10 to 200 leukocytes, predominantly mononuclear cells), mildly to moderately elevated protein levels, and hypochloremia. Additionally, measuring adenosine deaminase (ADA) levels in cerebrospinal fluid (CSF) can be a useful ancillary test for diagnosing central nervous system brucellosis.[15]

Imaging techniques, such as MRI and CT, can be useful in diagnosing brucellosis. However, these studies cannot provide a definitive diagnosis and may sometimes appear normal. The involvement of the sacroiliac joints is a strong indicator of brucellosis.[36] MRI may reveal high signal white matter lesions and enhancing lesions, potentially periventricular in meningoencephalitis. Meningitis and ventriculitis can also cause meningeal enhancement.[37] Scintigraphy can be useful in the context of brucellosis, aiding in the detection and assessment of various aspects of the infection. This imaging technique provides valuable information for diagnosis and treatment planning. Imaging plays a crucial role in identifying the manifestations of brucellosis in different body regions, allowing for appropriate and timely disease management.[38]

Histopathological examination of infections caused by *B. melitensis* and *B. abortus* may reveal non-caseating granulomas composed of epithelioid cells, polymorphonuclear leukocytes, lymphocytes, and some giant cells. Granulomas in *B. melitensis* infections are typically small, while *B. suis* infections often result in the formation of a chronic abscess accompanying the granulomas.[9]

The differential diagnosis for patients presenting with prolonged fever and osteoarticular involvement includes brucellosis, malaria, tuberculosis, visceral leishmania, endocarditis, HIV infection, enteric fever, malignancy, spondylitis, reactive arthritis, and septic arthritis. When examining histopathological samples, it is important to consider brucellosis, sarcoidosis, and fungal infections as potential causes of non-caseating granulomas.[8]

TABLE 1: Clinical classification of brucellosis.

Classification	Duration of symptoms before diagnosis	Major symptoms and signs	Diagnosis
Subclinical	-	Asymptomatic	Positive (low titer) serologic tests, negative cultures
Acute and subacute	Up to 2-3 months and 3 months-1 year	Malaise, chills, sweats, fatigue, headache, anorexia, arthralgias, fever, splenomegaly, lymphadenopathy, hepatomegaly	Positive serology, positive blood or bone marrow cultures
Localized	Occurs with acute or chronic untreated disease	Related to involved organs	Positive serologic tests, positive cultures in specific tissues
Relapsing	2-3 months after the initial episode	Same as an acute illness but may have a higher fever and more fatigue, weakness, chills, and sweats	Positive serologic tests, positive cultures
Chronic	>1 year	Nonspecific presentation but neuropsychiatric symptoms and low-grade fever most common	Low titer or negative serologic tests, negative cultures

TREATMENT

The primary objectives of brucellosis treatment are to alleviate symptoms, shorten symptomatic periods, and prevent complications, relapses, chronicity, and mortality (39, 40).

To achieve successful treatment, the following main principles should be followed: 1. Combination Therapy: Antimicrobial drug regimens for brucellosis should include at least two effective drugs.[39,41] Monotherapy for brucellosis is not recommended due to unacceptably high relapse rates.[41] 2. Intracellular Activity: The antimicrobial drugs selected must possess the capability to infiltrate macrophages and remain effective in the acidic intracellular environment where Brucella can survive. Additionally, treatment courses for brucellosis should be of sufficient duration to ensure complete eradication of the infection and minimize the risk of relapse.[39,41]

Commonly used antibiotics for the treatment of pediatric brucellosis include doxycycline, rifampin, aminoglycosides (such as streptomycin, gentamicin, and occasionally amikacin), and trimethoprim/sulfamethoxazole (TMP-SMX). The specific combination and duration of treatment depend on the severity of the infection and the patient's circumstances (Table 2).[39-41] TMP-SMX is preferred over doxycycline for children under 8 years old due to its side effects, especially tooth staining.[40,41]

Regimens that include a combination of aminoglycoside and doxycycline have shown higher cure rates compared to the doxycycline-rifampin regimen and are considered the gold standard for the treatment of brucellosis.[42] In a meta-analysis, it is reported that treatment failure and relapse in the doxycycline-rifampin combination is more common than in the doxycycline-aminoglycoside combination (18.2% vs. 6.7%; or 3.17, 95% CI (confidential interval) 2.05-4.91).[43]

For serious infections, such as endocarditis, meningitis, and osteoarticular involvement, the initial treatment should consist of a combination of three drugs. An aminoglycoside, such as streptomycin or gentamicin, is commonly administered for the first 7 to 14 days. Alongside the aminoglycoside, doxycycline or TMP-SMX (trimethoprim-sulfamethoxazole) in combination with rifampin should be given during the initial phase of treatment. After the first 7 to 14 days, the aminoglycoside is typically discontinued, but doxycycline or TMP-SMX, along with rifampin, is continued for a more extended duration, usually for 4 to 6 months (Table 3).[40]

Treatment for brucellosis-associated spondylitis is recommended to be more prolonged, typically around 12 weeks or even longer, using similar combinations of medications. In a study comparing treatment durations for brucellosis-associated spondylitis, treatment failure rates were 43% and 17% at 6 and 12 weeks, respectively. If persistent findings and radiological findings are present, treatment can be continued for more than 12 weeks. Surgery is an option if there is vertebral collapse, localized abscess or spinal instability, and persistence of neurological deficit (Table 3).[44]

TABLE 2: Regimens for treatment of brucellosis in children (in the absence of focal disease due to spondylitis, neurobrucellosis, or endocarditis).

Children ≥8 years	**Doxycycline** 4.4 mg/kg per day (maximum 200 mg/day) orally in 2 divided doses for 6 weeks **and** **Rifampin** 15-20 mg/kg per day (maximum 600-900 mg/day) orally once or twice daily for 6 weeks **Alternative Regimens** **Doxycycline** 4.4 mg/kg per day (maximum 200 mg/day) orally in 2 divided doses for 6 weeks **and** **Streptomycin** 15 to 40 mg/kg per day (maximum 1 g/day) intramuscularly or intravenously in 1-2 doses for the first 14-21 days **OR** **Gentamicin** 5 mg/kg/day intramuscularly or intravenously in 1 dose for 7-14 days
Children <8 years	**TMP-SMX** TMP 10 mg/kg per day (maximum 320 mg/day) and SMX 50 mg/kg per day (maximum 1.6 g/day) orally divided into 2 doses for 6 weeks **and** **Rifampin** 15-20 mg/kg per day (maximum 900 mg/day) orally once or ywice daily for 6 weeks

In the presence of neurobrucellosis, the recommended treatment includes a combination of doxycycline and rifampin for at least 12 weeks, with the addition of ceftriaxone for four-six weeks. The treatment duration can extend up to four to six months in most cases, and may even need to be continued for up to one year in severe cases. In a retrospective study that evaluated 215 neurobrucellosis patients, the addition of ceftriaxone or TMP-SMX to the doxycycline-rifampin combination was compared. The group where ceftriaxone was added showed a treatment failure and relapse rate of 3.6%, while the group where TMP-SMX was added had a rate of 14.3%.[45] An aminoglycoside, such as streptomycin or gentamicin, is commonly administered in combination with other therapies for the first 7 to 14 days (Table 3).[14,41,46]

In the presence of brucella endocarditis, antimicrobial treatment along with surgical intervention increases the chances of a successful cure. All these patients should undergo a surgical evaluation, and in the presence of heart failure, valve damage, abscess, or prosthetic valve, surgery should be applied. For antimicrobial treatment, a triple regimen consisting of aminoglycoside for 4 weeks and a combination of doxycycline-rifampin for at least 12 weeks is recommended. Depending on the clinical assessment and echocardiographic findings, the treatment may continue for up to 4-6 months (Table 3).[20]

Relapses are generally not caused by the emergence of antibiotic-resistant strains, although such cases have been observed after monotherapy with rifampicin or streptomycin. As a result, relapses can usually be managed by repeating the course of treatment using the same drugs. However, unlike relapse, managing chronic localized brucellosis might require surgical intervention to drain the foci of infection, in addition to antimicrobial therapy. This approach aims to effectively eliminate the source of infection and promote successful treatment. Interestingly, patients with delayed recovery may not benefit from undergoing repeated courses of antimicrobial therapy because persistence of symptoms may not be directly linked to the presence of active infection. The management of delayed recovery may require a more comprehensive approach that considers potential psychological factors contributing to the patient's condition.

Individuals who have consumed raw milk or raw milk products contaminated with the live attenuated cattle vaccine strain B. abortus strain RB51 are at high risk for brucellosis. To prevent the development of the disease, postexposure prophylaxis (PEP) is recommended if the person is still within the first six months of last exposure. PEP typically involves a combination of antibiotics such as doxycycline and trimethoprim-sulfamethoxazole. The standard PEP regimen is to administer these antibiotics for 21 days after the last exposure to the potentially contaminated products. Additionally, those at risk should be monitored for symptoms for a duration of 6 months following the last exposure to ensure early detection and management of any potential infection. It is important to note that B. abortus strain RB51 has developed resistance to certain antibiotics such as rifampin and penicillin. Therefore, these antibiotics should not be used in the treatment or prophylaxis of brucellosis caused by this particular strain. Taking

TABLE 3: Regimens for treatment of brucellosis in children.

For brucellosis-associated spondylitis and brucella endocarditis.[20,41,44]	
Children ≥8 years	**Doxycycline** 4.4 mg/kg per day (maximum 200 mg/day) orally in 2 divided doses for at least 12 weeks **and** **Rifampin** 15-20 mg/kg per day (maximum 600-900 mg/day) orally once or twice daily for at least 12 weeks and **Streptomycin** 15-40 mg/kg per day (maximum 1 g/day) intramuscularly or intravenously in 1-2 doses for the first 14-21 days (Brucella endocarditis, for the first 4 weeks) **OR** **Gentamicin** 5 mg/kg/day intramuscularly or intravenously in 1 dose for the first 7-14 days (Brucella endocarditis, for the first 4 weeks)
Children <8 years	**TMP-SMX** TMP 10 mg/kg per day (maximum 320 mg/day) and SMX 50 mg/kg per day (maximum 1.6 g/day) orally divided into 2 doses for at least 12 weeks **and** **Rifampin** 15-20 mg/kg per day (maximum 600-900 mg/day) orally once or twice daily for at least 12 weeks **and** **Streptomycin** 15-40 mg/kg per day (maximum 1 g/day) intramuscularly or intravenously in 1-2 doses for the first 14-21 days (Brucella endocarditis, for the first 4 weeks) **OR** **Gentamicin** 5 mg/kg/day intramuscularly or intravenously in 1 dose for the first 7-14 days (Brucella endocarditis, for the first 4 weeks)
For Neurobrucellosis[41,45]	
* Aminoglycoside should be administered along with the other treatments[42]	
Children ≥8 years	**Doxycycline** 4.4 mg/kg per day (maximum 200 mg/day) orally in 2 divided doses for at least 12 weeks **and** **Rifampin** 15-20 mg/kg per day (maximum 600-900 mg/day) orally once or twice daily for at least 12 weeks **and** **Ceftriaxone** 100 mg/kg/day divided every 12 hours (maximum 2 g per dose) for the first 4-6 weeks
Children <8 years	**TMP-SMX** TMP 10 mg/kg per day (maximum 320 mg/day) and SMX 50 mg/kg per day (maximum 1.6 g/day) divided into 2 doses for at least 12 weeks **and** **Rifampin** 15-20 mg/kg per day (maximum 900 mg/day) orally once daily for at least 12 weeks **and** **Ceftriaxone** 100 mg/kg/day divided every 12 hours (maximum 2 g per dose) for the first 4-6 weeks

prompt and appropriate measures in case of exposure to potentially contaminated products can significantly reduce the risk of developing brucellosis and help prevent the spread of the infection.[47]

FOLLOW-UP

In general, routine serological tests are not sufficient for evaluating the treatment process and distinguishing between active and recent brucellosis infections. It is essential to differentiate between active and recent infections serologically, which may not always be feasible. When interpreting serological tests during follow-up, it is crucial to consider the current clinical findings and the patient's treatment history.[48,49]

PREVENTION

As of now, there is no vaccine available for the prevention of brucellosis in humans. To prevent the disease, measures such as pasteurization of dairy products, reducing occupational exposure risk, preventing person-to-person transmission, and controlling the disease in animals are essential.[1,2]

In cases where a mother has been diagnosed with untreated brucellosis, it is recommended that she discontinue breastfeeding. The reason for this precaution is to avoid the potential transmission of the *Brucella* bacteria to the baby through breast milk. Instead of breastfeeding directly, the mother should maintain her breast milk supply by regularly pumping and discarding the milk to prevent potential con-

tamination. During this period, it is advised that the infant receives pasteurized donor human milk or infant formula as an alternative source of nutrition until breastfeeding can safely resume. After the mother has received at least 48-96 hours of antibiotic treatment for brucellosis, the risk of transmission through breast milk decreases significantly. However, it is essential to note that stored milk that might have been collected before antibiotic treatment should be discarded unless samples have been tested and found to be negative for the *Brucella* organism. Taking these precautions helps ensure the safety and health of the infant and prevents the spread of the infection through breast milk.[50]

CONCLUSION

Brucellosis is one of the most common zoonotic infections worldwide and represents a significant public health problem throughout the world, especially in resource-limited countries. Source control is important to prevent brucellosis infection and its complications. For our country, which is in the endemic region, it is necessary to inform the health care professionals and the public about brucellosis in order to prevent the delay in the diagnosis and treatment, and its consequences.

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