

Original Article

Testicular involvement of Brucellosis: a 10-year, multicentre study

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Abstract

Introduction: The genito-urinary system is one of the most common areas of involvement in brucellosis. To present the epidemiological, clinical, and laboratory characteristics of patients with testicular involvement associated with brucellosis, together with the diagnostic and therapeutic approaches.

Methodology: Patients followed up for brucellosis-related testicular involvement between January 2012 and November 2022 were included in the study. Brucellosis is defined as the production of *Brucella* spp. in cultures, or clinical symptoms together with the serum standard tube agglutination test titer of $\geq 1/160$. Inflammation in scrotal Doppler ultrasonography was based on testicular involvement.

Results: A retrospective evaluation was made of the data of 194 patients with brucellosis-related testicular involvement. The rate of determination of testicular involvement in brucellosis was 2.57%. The most affected patients were determined in the 16-30 years age range. On presentation, brucellosis was in the acute stage in 83.7% of patients. The most common symptoms on presentation were swelling and/or pain in the testes (86.6%). In the patients where a spermogram could be performed, oligospermia was determined in 41.7%, and aspermia in 8.3%. When the testicular involvement of brucellosis was evaluated, epididymo-orchitis was present at the rate of 55.7%, epididymitis at 27.3%, and testis abscess at 5.1%.

Conclusions: Although epididymo-orchitis was the most frequently determined form of involvement in this study, there was also seen to be a significant number of patients presenting with epididymitis. Male patients presented with the clinical status of brucellosis should be questioned about swelling and pain in the testes to avoid overlooking testicular involvement.

Key words: Brucellosis; epididymo-orchitis; testis; oligospermia.

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Introduction

Brucellosis is one of the most common zoonotic infections caused by species of the *Brucella* genus [1]. It is endemic in countries in the Mediterranean region, the Middle East, China, the Far East, the Indian subcontinent, Mexico, some regions of Central and South America, and sub-Saharan Africa [2]. Although approximately 500,000 cases are reported each year throughout the world, this number is believed to be higher [3]. Brucellosis is the most commonly seen zoonotic infection in Turkey, primarily in the East, Southeast, and Central Anatolian regions [4]. Infection

is spread through the consumption of unpasteurized milk or other dairy products, or through direct contact with an infected animal, placenta, or aborted fetus [5].

Brucellosis manifests clinically as listlessness, fever, joint pains, and night sweats with an insidious onset. Symptoms and findings such as weight loss, low back pain, headache, dizziness, anorexia, abdominal pain, dyspepsia, cough, and depression, may also be seen [2,6]. Diagnosis is made from culture, serology, and nucleic acid amplification tests. Bone marrow and blood cultures are the gold standard in diagnosis [7]. Through the hematogenous route, *Brucella* spp. spread

to the reticuloendothelial system, localized primarily in the joints, central nervous system, cardiovascular system, respiratory system, and genito-urinary system [8]. The genito-urinary system is one of the most common areas of involvement of brucellosis, with symptoms seen such as epididymo-orchitis, cystitis, prostatitis, pyelonephritis, interstitial nephritis, exudative glomerulonephritis, immunoglobulin A nephropathy, kidney, and testis abscesses. Especially, epididymo-orchitis is the most frequently seen finding and was first described by Hardy and Wainwright in 1928-1929 [3]. The aim of this retrospective study was to present the epidemiological, clinical, and laboratory characteristics and diagnostic and therapeutic approaches to patients with testicular involvement associated with brucellosis. This study can be considered to make a valuable contribution to literature as it includes a large patient population of brucellosis-related testicular involvement.

Methodology

Study protocol

This retrospective, multi-center study included patients aged > 16 years, who were being followed up in the Infectious Diseases and Clinical Microbiology Clinics of nine hospitals in different regions of Turkey, between January 2012 and November 2022 due to brucellosis-related testicular involvement. The information on the patients was retrieved from the hospital information system. Evaluations were made with respect to age, occupation, place of residence, history of brucellosis, history of consumption of unpasteurized milk or other dairy products, clinical symptoms, comorbidities, laboratory test results, and treatment approaches.

Bacteriological and serological identification

Two sets of blood cultures were taken from the patients and inoculated into an aerobic bottle. Blood cultures were incubated in a blood culture device (BACT/ALERT 3D, France) for five days. The bottles with positive signals were planted on sheep blood agar (RTA, Turkey) and chocolate agar (RTA, Turkey). Growing colonies were identified by matrix-assisted laser desorption ionization time of flight mass spectrometry (MALDI-TOF MS) (VITEK MS, France). As a serological test, the serum standard tube agglutination method (Wright test, Biomedica, Canada) was performed using *Brucella abortus* S.99 antigen. Primary dilution was started in 1/20 tube, final dilution was made up to 1/5120. Wright test titer $\geq 1/160$ was considered positive.

Definitions

Brucellosis is defined as the production of *Brucella* spp. in blood or other bodily fluid cultures, or clinical symptoms together with the serum standard tube agglutination (STA) test titer of $\geq 1/160$, or a 4-fold increase in titer in serum samples taken at a 2-week interval.

Brucellosis classification; Patients were categorized into 3 groups according to the duration of clinical signs and symptoms, acute: 0-2 months, subacute: 2-12 months, and chronic brucellosis: > 12 months [4].

Testicular involvement was defined as the determination of epididymitis, orchitis, epididymo-orchitis, or testis abscess on scrotal color Doppler ultrasonography (USG) together with clinical symptoms related to the genital region (pain, swelling, temperature increase in the testis). Relapse was defined as the recurrence of clinical signs and symptoms within 12 months of the completion of brucellosis treatment [8].

Ethics Committee Approval

Approval for the study was granted by the Clinical Research Ethics Committee of Harran University (decision no: 2022/16/04, dated: 22.08.2022). All the study procedures were performed in compliance with the Helsinki Declaration.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS version 22.0 software (SPSS Inc, Chicago, IL, USA). The conformity of continuous variables to normal distribution was tested with the One-Sample Kolmogorov-Smirnov test. All continuous variables were stated as mean \pm standard deviation values. The Student's t-test was applied in the comparisons of two groups of continuous variables showing normal distribution and the Mann-Whitney U-test was used when the distribution was not normal. For the comparisons of more than two groups, the One-Way ANOVA test was applied for those with normal distribution and the Kruskal Wallis test for continuous variables not showing normal distribution. To determine from which group the difference originated when a significant difference was determined, multiple comparisons were applied when normal distribution assumptions were met, and the Mann-Whitney U-test was used when normal distribution assumptions were not met. For all analyses, a value of $p < 0.05$ was accepted as statistically significant.

Results

Evaluations were made of a total of 194 patients with testicular involvement associated with brucellosis. From the total of 7530 male patients diagnosed with brucellosis in the defined study period, testicular involvement was determined in 2.57%. The mean age of the patients was 34.66 ± 14.54 years (range, 16-91 years), and patients in the 16-30 years age range were determined to be most affected (n = 91, 46.9%) (Figure 1). The most presentations were seen to be in 2019 (n = 32, 16.49%) and according to months, the most presentations were in July (n = 25, 12.89%) (Figure 2).

The mean duration of symptoms before diagnosis was 30.51 ± 23.69 days. With respect to occupations, farmers were determined to be most affected (n = 59, 53.1%) and the vast majority of patients (n = 117, 60.3%) lived in a rural area. Of the 57 (41.3%) patients with a history of brucellosis, 51 (89.5%) stated that they had previously received treatment for brucellosis. Patients with a previous history of brucellosis were most likely to present with acute (n = 33, 57.8%) and chronic (n = 9, 15.7%) stages of brucellosis during new brucellosis episodes. Of the significant routes of infection, 91 (67.4%) patients stated that they had consumed unpasteurized fresh cheese (Table 1).

Of the patients who could be categorized, 134 (83.7%) were classified as acute, 26 (16.3%) as subacute, and there were no patients in the chronic brucellosis group. When the testicular involvement of brucellosis was evaluated, epididymo-orchitis was determined in 108 (55.7%) patients, epididymitis in 53 (27.3%), and testis abscess in 10 (5.1%). The mean duration of symptoms before diagnosis in the patients determined with testis abscess was 30.20 ± 17.22 days. Right-side testis involvement was determined in 106 (54.6%) patients and bilateral involvement was observed in 12 (6.2%) (Table 2).

Table 1. Epidemiological characteristics of patients.

Variables	n (%)
Occupation group	
Self-occupation	28 (25.2)
Farmer	59 (53.1)
Others	24 (21.7)
Lived in	
City center	77 (39.7)
Rural area	117 (60.3)
History of brucellosis	57 (41.3)
Previously received treatment for brucellosis	51 (89.5)
Family history of brucellosis	67 (48.9)
Abortion in animals	40 (33.3)
Herbed cheese consumption	24 (17.8)
Unpasteurized fresh cheese consumption	91 (67.4)
Raw Milk Consumption	15 (11.1)

Figure 1. Age distribution of patients.

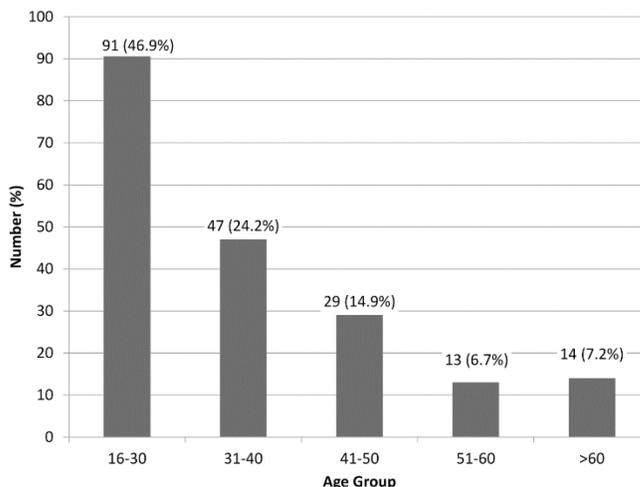


Figure 2. Distribution of patient presentations by months.

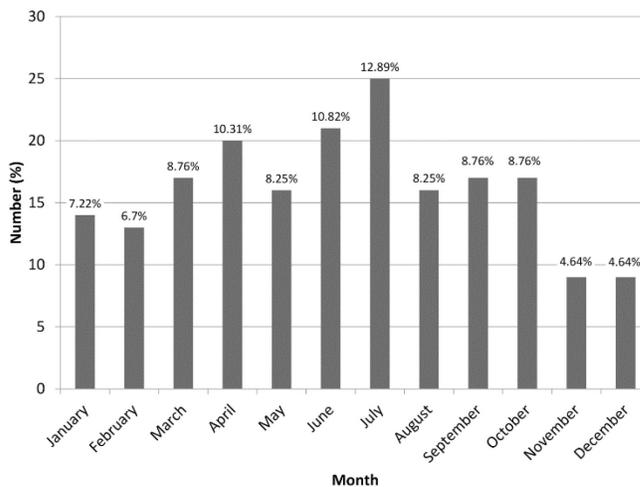


Table 2. Brucellosis subgroups classification and types of testicular involvement.

Characteristics	n (%)
Type of testicular involvement	
Epididymitis	53 (27.3)
Orchitis	24 (12.4)
Epididymo-orchitis	107 (55.2)
Testis abscess	8 (4.1)
Orchitis + Testis abscess	1 (0.5)
Epididymo-orchitis + Testis abscess	1 (0.5)
Epididymo-orchitis (total)	108 (55.7)
Orchitis (total)	25 (12.9)
Testis abscess (total)	10 (5.1)
Involved testicular localization	
Right (only)	106 (54.6)
Left (only)	76 (39.2)
Bilateral	12 (6.2)
Brucellosis subgroups	
Acute	134 (83.7)
Subacute	26 (16.3)
Chronic	0 (0.0)

Table 3. Distribution of clinical symptoms and signs.

General symptoms	n (%)	Genitourinary system symptoms	n (%)
Fever	97 (69.8)	Dysuria	47 (34)
Chills	86 (62.3)	Urination frequency	29 (21)
Sweating	90 (65.2)	Urethral discharge	2 (1.4)
Widespread joint/muscle pain	101 (73.2)	No symptom	52 (37.7)
Loss of appetite	101 (73.7)	Swelling in the testis	168 (86.6)
Nausea	66 (48.2)	Pain in the testis	168 (86.6)
Vomiting	19 (14.1)		
Headache	41 (30.1)		
Weight loss	50 (36.8)		

The most frequently described general symptoms of the patients on presentation were loss of appetite (n = 101, 73.7%), widespread joint/muscle pain (n = 101, 73.7%), and fever (n = 97, 69.8%). The most frequently described genito-urinary system symptoms were swelling and/or pain in the testis (n = 168, 86.6%), and dysuria (n = 47, 34%), and 52 (37.7%) patients had no urinary system symptoms (Table 3).

The pathological findings most frequently determined in the laboratory tests were elevations in C-reactive protein (CRP) (n = 147, 78.60%), erythrocyte sedimentation rate (ESR) (n = 111, 66.86%), and alanine aminotransferase (ALT) (n = 84, 43.97%) (Table 4). In the full urine analysis, microscopic hematuria was observed at the rate of 17.4% (20/115) pyuria at 11.3% (13/115), and test results were normal in 71.3% (82/115) of the patients. Of the 12 patients for whom a spermogram was performed, oligospermia was determined in 5 (41.7%), aspermia in 1 (8.3%), and the results of 6 (50%) were normal. Of the patients with pathological spermogram findings, testis abscess was present in 3, epididymo-orchitis in 2, and orchitis in 1.

When the diagnostic tests for brucellosis were evaluated, positivity rates were determined in the Rose Bengal test at 99.5% (192/193) and in the STA test at 98.5% (191/194). Blood culture was performed in 25.25% (49/194) of the cases, and *Brucella* spp. were grown in the cultures of 30.6% (15/49) of these patients. Orchiectomy was performed in 3 (1.54%) patients and testis biopsy in 5 (2.57%) of the patients, and the pathology results of these patients was granulomatous

inflammation in 7 (87.5%) and abscess formation in 1 (12.5%) patient.

The most frequently applied drug combinations in brucellosis treatment were doxycycline plus rifampicin (n = 77, 40.1%) and doxycycline plus streptomycin for two weeks followed by doxycycline plus rifampicin (n = 66, 34.4%). Treatment was administered to the patients for a mean 9.10 + 3.30 weeks (range 6-12 weeks). The treatment was changed in 7.2% (13/180) of cases because of various side effects. Relapse was seen in 5 (5.57%) patients after terminating the antibiotics, and it was determined that 4 of these patients had previously received treatment for 6 weeks and 1 for 12 weeks.

Discussion

Epididymo-orchitis is one of the most frequently seen complications of brucellosis in the male genito-urinary system. As the epididymis and the testis are joined to each other, both components are usually affected in inflammation [9]. In some studies, conducted in regions where brucellosis is endemic, the frequency of epididymo-orchitis has been determined in the range of 3.1%-11.1% [10-15]. In a multicenter study by Erdem et al. [8], genito-urinary system involvement of brucellosis was examined, and epididymo-orchitis (58%) and orchitis (31.8%) were determined most often in male patients, and epididymitis alone was seen less often on presentation (3.1%). In the same study, testis abscess was determined at the rate of 1.7%. In a case series reported by Bosilkovski et al. [14], orchitis was determined most often, the left testis was more affected,

Table 4. Laboratory findings of the patients.

Laboratory findings	n			Laboratory findings	n		
	(+)	Total	%		(+)	Total	%
CRP elevation (> 5 mg/L)	147	187	78.60	Lymphocytosis (> 11,000/ mm ³)	36	193	18.65
ESR elevation (> 20 mm/h)	111	166	66.86	Creatine elevation (> 1.2 mg/dl)	14	188	7.44
ALT elevation (> 41 U/L)	84	191	43.97	Thrombocytopenia (< 150,000/mm ³)	8	193	4.14
AST elevation (> 31 U/L)	66	191	34.55	Leukopenia (< 4,000/mm ³)	5	193	2.59
Hypoalbuminemia (< 3.5 g/dL)	39	113	34.51	Thrombocytosis (> 400,000/mm ³)	4	193	2.07
Anemia (< 13 g/dL)	56	193	29.01	Lymphopenia (< 1,000/mm ³)	4	193	2.07
Leukocytosis (> 11,000/ mm ³)	44	193	22.79	Neutropenia (< 1,500/mm ³)	1	193	0.51

and the rate of bilateral involvement was 14.7%. A study in Iran reported that epididymo-orchitis was determined at the rate of 50.9%, orchitis at 49.1%, epididymitis was not determined, and bilateral involvement was observed in only one case [16]. The results of the current study showed that testicular involvement of brucellosis was determined at the rate of 2.57%, epididymo-orchitis (55.7%) and epididymitis were determined most often and testis abscess was seen in 5.1%. The right testis was affected more and bilateral involvement was seen in 6.2%. It was a striking finding that epididymis involvement alone was determined at a higher rate than the literature.

Epididymo-orchitis is seen more often in the acute stage of brucellosis, and rarely in the subacute and chronic stages [14,17-20]. Clinically, genito-urinary symptoms and findings such as unilateral scrotal redness, swelling, pain, dysuria, and the presence of abnormal urethral secretions are seen together with general systemic symptoms such as fever and shivering [9]. In countries where the disease is endemic, individuals in the age range of 15-35 years, in particular, are more affected [4]. Colmonero *et al.* [11] reported the mean duration of symptoms before diagnosis to be 52.5 days, the most frequently described complaints were high fever (100%), swelling/pain in the scrotum (100%), and shivering (87.5%), urinary symptoms were only determined in 4.2%, and males in the 14-30 years age range were most affected. In another study by Navarro-Martinez *et al.* [21], the mean age of patients was reported to be 34 years, an acute onset was seen in 78%, and the most common complaints were scrotal pain/swelling (100%), fever (88%), and sweating (73%). Güneş *et al.* [22] reported that the mean age of patients was 27 ± 3.5 years, 87% of patients presented in the acute stage of brucellosis, and the most common complaints were testicular pain and swelling (100%), high fever (93%), and fatigue (93%). In the current study, the mean patient age was 34.66 ± 14.54 years, with most affected patients (46.9%) in the 16-30 years age range, 83.7% presented in the acute period of brucellosis, and the most common complaints were determined to be swelling/pain in the testis (86.6%), loss of appetite (73.7%), widespread joint/muscle pain (73.2%) and fever (69.8%). A vast majority of the complaints on presentation were related to the genital system and the fact that brucellosis is endemic in our region was a guiding factor in the diagnosis. In addition, the practice of clinicians requesting serological testing for brucellosis in addition to the general laboratory tests could be another important factor facilitating diagnosis.

The definitive diagnosis of brucellosis is made by bacterial isolation from blood, bone marrow, or other tissue cultures. Culture positivity in microbiologic samples varies between 15% and 90%. When bacterial isolation is not possible, serology is the preferred diagnostic method and is widely used [4]. In a study conducted by Erdem *et al.* [8], the Rose Bengal test was 91.6% positive, the STA test was 94% positive, the Coombs STA test was 92.9% positive, the blood culture was 36.5%, the bone marrow culture was 63.6%, genital discharge culture 5.9% and urine culture 1.5%. Roushan *et al.* [16] reported STA test positivity in all patients diagnosed with brucellosis epididymo-orchitis and 38.1% of blood cultures showed production. Navarro-Martinez *et al.* [21] observed 93% positivity in the Coombs STA test and growth in 69% of blood cultures. In the current study, similar to the findings in the literature, positivity was determined at the rate of 99.5% in the Rose Bengal test and 98.5% in the STA test, and *Brucella* spp. was produced in 30.6% of the blood cultures. As bone marrow culture is a difficult procedure for both the patient and the clinician, it is not routinely performed, but when a microbiology laboratory is available, blood culture can be easily performed. One of the important limitations of this study is that blood culture was only taken from one in four patients. Although the serological test results are reliable in a general sense, greater weight should be given to the taking of blood culture as it is the gold standard method.

Anemia, leukopenia, thrombocytopenia, elevated liver enzymes, and CRP are the most significant laboratory findings, especially in acute and subacute brucellosis. In addition, an increase in ESR levels and lymphomonocytosis can be seen in all clinical sub-forms [4]. In the study by Güneş *et al.* [22], leukocytosis, and elevated ESR, AST, and ALT were determined most often. Savaşçı *et al.* [23] reported the most frequently observed laboratory findings as leukocytosis and elevated CRP and ESR. In brucellosis epididymo-orchitis, urine analysis may not be very significant. Colmonero *et al.* [11] observed proteinuria, hematuria, pyuria, or some combinations of these in only 32% of patients. In the current study, the most frequently determined laboratory findings were elevated CRP, ESR, and ALT. Microscopic hematuria and pyuria were seen at a low level in the full urine analysis. These general laboratory findings were seen to be in parallel with the literature. When it is considered that the presence of hematuria and pyuria in the full urine analysis could be a sign of inflammation or damage in the genito-urinary tract, it could be a

supportive finding, but it must not be forgotten that a differential diagnosis will be needed as these could develop for several etiological reasons.

Brucella epididymo-orchitis can lead to reduced or even complete loss of male sexual function. By significantly affecting the amount and quality of sperm, epididymitis can lead to azoospermia and sperm death [9]. In a study by Akinci *et al.* [24], sperm analysis was determined to be below normal in almost all the patients in the acute phase of brucellosis, but after treatment, permanent aspermia or oligospermia was seen in some patients. Spermogram was performed in only 6.8% of the current study patients, and of these, oligospermia was determined in 41.7%, aspermia in 8.3%, and there were no pathological findings in 50%. Although it was a highly significant finding that the amount of sperm was affected in almost half of the patients, as the sample size was low there is a need for further studies with larger patient populations. However, there can be considered to be evidence from this study that there is a need to perform spermogram at certain intervals after the completion of treatment to evaluate the permanent effects of brucellosis on the amount, function, and quality of sperm.

The treatment of *brucella* epididymo-orchitis and the treatment of classic brucellosis are almost the same and should be administered for at least 45 days [8,25]. However, there are studies in the literature reporting a treatment duration of 8 or 12 weeks [8,10,11,16,17]. The World Health Organisation (WHO) recommends brucellosis treatment of a combination of rifampicin (600-900 mg/day) + doxycycline (2 × 100 mg/day) for 45 days or a combination of doxycycline (2 × 100 mg/day) for 45 days and streptomycin (1 × 1 gr/day) for 15 days [26]. Relapse is seen in 5-15% of patients following treatment, which generally occurs within the first 6 months after completing treatment but may also be seen after 12 months [27-30]. Although brucellosis epididymo-orchitis generally has a good prognosis, deficiencies in treatment can lead to severe complications such as testis abscess, which will require orchiectomy [21]. In the current study, the most frequently applied treatment combinations were doxycycline plus rifampicin (40.1%), and 2 weeks of doxycycline + streptomycin followed by doxycycline plus rifampicin (34.4%). Treatment was applied to the patients for a mean of 9 weeks. Orchiectomy was performed in only 1.54% of the patients because of testis abscess. Relapse developed in 2.57% of the patients after the termination of the antibiotics.

There were some limitations to this study, including the retrospective design and that some data obtained

from other centers may have been incomplete. The low rates of blood culture and spermogram and that USG and spermogram were not repeated to determine whether or not there were permanent changes after treatment can also be considered limitations.

Conclusions

Brucellosis is an endemic disease in Turkey and one of the important regions of focal involvement is the testes. The early diagnosis and treatment of epididymo-orchitis are extremely important to be able to prevent the development of permanent changes. The results of the current study showed that patients in the young adult group were most affected, there were more presentations at the acute brucellosis stage, and although epididymo-orchitis was the form of involvement determined most, there were also seen to be presentations with the clinical form of epididymitis. In patients where spermogram could be performed, the determination of oligospermia or aspermia at a high rate was a noteworthy finding. Patients presenting with clinical brucellosis must be questioned about testis swelling and pain, and testicular involvement must not be overlooked. It must also not be forgotten that a delay in diagnosis can lead to a more complicated condition such as testis abscess which will require an orchiectomy.

References

- Lai S, Chen Q, Li Z (2021) Human Brucellosis: an ongoing global health challenge. *China CDC Wkly* 3: 120-123. doi: 10.46234/ccdcw2021.031.
- Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV (2006) The new global map of human brucellosis. *Lancet Infect Dis* 6: 91-9. doi: 10.1016/S1473-3099(06)70382-6.
- Bosilkovski M, Dimzova M, Grozdanovski K (2009) Natural history of brucellosis in an endemic region in different time periods. *Acta Clin Croat* 48: 41-6.
- Buzgan T, Karahocagil MK, Irmak H, Baran AI, Karsen H, Evirgen O, Akdeniz H (2010) Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. *Int J Infect Dis* 14: 469-478. doi: 10.1016/j.ijid.2009.06.031.
- Dean AS, Crump L, Greter H, Schelling E, Zinsstag J (2012) Global burden of human brucellosis: a systematic review of disease frequency. *Plos Negl Trop Dis* 6: e1865. DOI: 10.1371/journal.pntd.0001865.
- Young EJ (1995) Brucellosis: current epidemiology, diagnosis, and management. *Curr Clin Top Infect Dis* 15: 115-28.
- Yagupsky P, Morata P, Colmenero JD (2019) Laboratory diagnosis of human brucellosis. *Clin Microbiol Rev* 33: e00073-19. doi: 10.1128/CMR.00073-19.
- Erdem H, Elaldi N, Ak O, Gulsun S, Tekin R, Ulug M, Duygu F, Sunnetcioglu M, Tulek N, Guler S, Cag Y, Kaya S, Turker N, Parlak E, Demirdal T, Ataman Hatipoglu C, Avci A, Bulut C, Avci M, Pekok A, Savasci U, Kaya S, Sozen H, Tasbakan

- M, Guven T, Bolukcu S, Cesur S, Sahin-Horasan E, Kazak E, Denk A, Gonen I, Karagoz G, Haykir Solay A, Alici O, Kader C, Senturk G, Tosun S, Turan H, Baran AI, Ozturk-Engin D, Bozkurt F, Deveci O, Inan A, Kadanali A, Sayar MS, Cetin B, Yemisen M, Naz H, Gorenek L, Agalar C (2014) Genitourinary brucellosis: results of a multicentric study. *Clin Microbiol Infect* 20: 847-853. doi: 10.1111/1469-0691.12680.
9. Yu J, Li S, Wang L, Dong Z, Si L, Bao L, Wu L (2022) Pathogenesis of *Brucella* epididymo-orchitis-game of *Brucella* death. *Crit Rev Microbiol* 48: 96-120. doi: 10.1080/1040841X.2021.1944055.
 10. Yetkin MA, Erdinc FS, Bulut C, Tulek N (2005) Epididymo-orchitis due to brucellosis in central Anatolia, Turkey. *Urol Int* 75: 235-238. doi: 10.1159/000087801.
 11. Colmenero JD, Munoz-Roca NL, Bermudez P, Plata A, Villalobos A, Reguera JM (2007) Clinical findings, diagnostic approach, and outcome of *Brucella melitensis* epididymo-orchitis. *Diagn Microbiol Infect Dis* 57:367-372.
 12. Zheng R, Xie S, Lu X, Sun L, Zhou Y, Zhang Y, Wang K (2018) A systematic review and meta-analysis of epidemiology and clinical manifestations of human brucellosis in China. *Biomed Res Int* 2018: 1-10. doi: 10.1155/2018/5712920.
 13. Najafi N, Ghassemian R, Davoody AR, Tayebi A (2011) An unusual complication of a common endemic disease: clinical and laboratory aspects of patients with brucella epididymo-orchitis in the north of Iran. *BMC Res Notes* 4: 1-4. doi: 10.1186/1756-0500-4-286.
 14. Bosilkovski M, Kamiloski V, Miskova S, Balalovski D, Kotevska V, Petrovski M (2018) Testicular infection in brucellosis: Report of 34 cases. *J Microbiol Immunol Infect* 51: 82-87. doi: 10.1016/j.jmii.2016.02.004.
 15. Çalık Ş, Gökengin AD (2011) Human brucellosis in Turkey: a review of the literature between 1990 and 2009. *Turk J Med Sci* 41: 549-555. doi: 10.3906/sag-0911-404.
 16. Hasanjani Roushan MR, Baiani M, Javanian M, Kasaeian AA (2009) Brucellar epididymo-orchitis: review of 53 cases in Babol, northern Iran. *Scand J Infect Dis* 41: 440-444. DOI: 10.1080/00365540902968043.
 17. Celen MK, Ulug M, Ayaz C, Geyik MF, Hosoglu S (2010) Brucellar epididymo-orchitis in southeastern part of Turkey: an 8 year experience. *Braz J Infect Dis* 14: 109e15. doi: 10.1016/S1413-8670(10)70021-0.
 18. Stamatiou K, Polyzois K, Dahanis S, Lambou T, Skolarikos A (2009) *Brucella melitensis*: a rarely suspected cause of infections of genitalia and the lower urinary tract. *Braz J Infect Dis* 13: 86-89.
 19. Karakose A, Yuksel MB, Aydogdu O, Hamidi AA (2013) Epididymo-orchitis as the first finding in patients with brucellosis. *Adv Urol* 2013: 765023. doi: 10.1155/2013/765023
 20. Memish ZA, Venkatesh S (2001) Brucellar epididymo-orchitis in Saudi Arabia: a retrospective study of 26 cases and review of the literature. *BJU Int* 88: 72-76. doi: 10.1046/j.1464-410x.2001.02243.x.
 21. Navarro-Martinez A, Solera J, Corredoira J, Beato JL, Alfaro EM, Atiénzar M, Ariza J (2001) Epididymo-orchitis due to *Brucella melitensis*: a retrospective study of 59 patients. *Clin Infect Dis* 33: 2017-2022. doi: 10.1086/324489.
 22. Güneş M, Geçit İ, Bilici S, Demir C, Özkal A, Ceylan K, Karahocagil MK (2010) Brucellar epididymo-orchitis: report of fifteen cases. *Van Med J* 17: 131-135.
 23. Savasci U, Zor M, Karakas A, Aydin E, Kocaaslan R, Oren NC, Eyigun CP (2014) Brucellar epididymo-orchitis: a retrospective multicenter study of 28 cases and review of the literature. *Travel Med Infect Dis* 12: 667-672. doi: 10.1016/j.tmaid.2014.10.005.
 24. Akıncı E, Bodur H, Çevik MA, Erbay A, Eren SS, Zıraman İ, Ergül G (2006) A complication of brucellosis: epididymo-orchitis. *Int J Infect Dis* 10: 171-177.
 25. Papatsoris AG, Mpadra FA, Karamouzis MV, Frangides CY (2002) Endemic brucellar epididymo-orchitis: a 10-year experience. *Int J Infect Dis* 6: 309-313. doi: 10.1016/S1201-9712(02)90166-9.
 26. Corbel MJ (2006) Brucellosis in humans and animals. WHO. 2006. p. 1-102. Available: <https://www.who.int/publications/i/item/9789241547130>. Accessed: 13 Feb 2023.
 27. Ariza J, Bosilkovski M, Cascio A, Colmenero JD, Corbel MJ, Falagas ME, Memish ZA, Roushan MR, Rubinstein E, Sipsas NV, Solera J, Young EJ, Pappas G, International Society of Chemotherapy, Institute of Continuing Medical Education of Ioannina (2007) Perspectives for the treatment of brucellosis in the 21st century: the Ioannina recommendations. *PLoS Med* 4: e317. doi: 10.1371/journal.pmed.0040317.
 28. Ariza J, Corredoira J, Pallares R, Viladrich PF, Rufi G, Pujol M, Gudiol F (1995) Characteristics of and risk factors for relapse of brucellosis in humans. *Clin Infect Dis* 20: 1241-9. doi: 10.1093/clinids/20.5.1241.
 29. Roushan MR, Gangi SM, Ahmadi SA (2004) Comparison of the efficacy of two months of treatment with co-trimoxazole plus doxycycline vs. co-trimoxazole plus rifampin in brucellosis. *Swiss Med Wkly* 134: 564-8. doi: 10.4414/smw.2004.10665.
 30. Solera J, Martínez-Alfaro E, Espinosa A (1997) Recognition and optimum treatment of brucellosis. *Drugs* 53: 245-56. doi: 10.2165/00003495-199753020-00005.

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