

# Brucellar epididymo-orchitis in southeastern part of Turkey: an 8 year experience

## ABSTRACT

**Objective:** the different clinical and laboratory features and response to treatment of patients with acute brucellar epididymo-orchitis (BEO) reporting to the reference hospital in Southeastern Anatolia of Turkey. **Material and methods:** in this study, 27 male patients with brucellosis, who presented with epididymitis or epididymo-orchitis (EO) at the university hospital in Diyarbakir from 1998 to 2006, were included. They were compared with the other male patients. Positive blood culture or high agglutination titers of  $\geq 1/160$  and positive clinical manifestations of brucellosis were the main criteria for diagnosing brucellosis. **Results:** fourteen patients had unilateral EO. Leukocytosis was present in 10 patients; all of them had initial agglutination titers of  $\geq 1/160$  and 10 patients had a positive blood culture. All patients received combined therapy with streptomycin for the first 21 days (or oral rifampicin for 6-8 weeks) with doxycycline or tetracycline for 6-8 weeks. All showed improvement, fever subsided in 3-7 days, and the scrotal enlargement and tenderness regressed. Only one patient had a relapse within one year. **Conclusion:** in brucellosis-endemic areas, clinicians encountering EO should consider the likelihood of brucellosis. In this study, young age was the most common risk factor, and leukocytosis and high CRP level were the most common laboratory findings. Most cases were unilateral. All patients responded to medical management very well. Conservative management with combination antibiotic therapy was adequate for managing BEO. Conclusively, brucellosis must be considered as a cause of orchitis, especially in endemic regions like Turkey.

**Keywords:** epididymo-orchitis, brucellosis, Turkey, medical treatment.

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## INTRODUCTION

Brucellosis is a zoonosis widely distributed worldwide. Millions of individuals are at risk throughout the world, especially in developing countries in which infection in animals is not under control. Although the current incidence of brucellosis in developed countries is low, it occurs sporadically in occupationally exposed groups, including farmers, veterinarians, and laboratory and slaughterhouse workers.<sup>1,2</sup>

Brucellosis is an endemic disease in Turkey. The incidence of this disease in our country is 23 per 100,000 yearly.<sup>3</sup> It is frequent especially in the rural areas of the middle and southeastern regions, and *Brucella melitensis* is the most prevalent strain.<sup>4</sup> The disease typically attacks young and middle-aged adults, with a low incidence among infants and elderly patients.<sup>5</sup> It has high degree of morbidity for humans, and has caused significant economic

loss, representing a serious public health problem in many developing countries.<sup>6</sup>

In humans, brucellosis behaves as a systemic infection with a very heterogeneous clinical spectrum. The most frequent symptoms are fever, chills or rigors, malaise, generalized ache, headache, and fatigue. The prevalence and pattern of complications depend on strain of brucella infecting the individual, age of the patient, and duration of disease.<sup>7</sup> Gastrointestinal, skeletal, cardiovascular, genitourinary, and hematological manifestations are well known. Neurobrucellosis, peritonitis, pericarditis, and pancytopenia are unusual manifestations of brucellosis.<sup>8,9</sup> If the disease is not well recognized and not included in the differential diagnosis, a treatable disease will be missed.<sup>9</sup>

In men, various genitourinary infections including epididymo-orchitis (EO), prostatitis, cystitis, pyelonephritis, interstitial nephritis, exudative glomerulonephritis, renal and tes-

## Authors

Mustafa Kemal Celen<sup>1</sup>  
 Mehmet Uluğ<sup>2</sup>  
 Celal Ayaz<sup>3</sup>  
 Mehmet Faruk Geyik<sup>4</sup>  
 Salih Hosoglu<sup>5</sup>

<sup>1</sup>Dicle University Medical School, Department of Infectious Diseases and Clinic Microbiology, 21280 Diyarbakir, Turkey.

<sup>2</sup>BSK Anadolu Hospital, Department of Infectious Diseases and Clinic Microbiology, 43100 Kütahya, Turkey.

<sup>3</sup>Dicle University Medical School, Department of Infectious Diseases and Clinic Microbiology, 21280 Diyarbakir, Turkey.

<sup>4</sup>Düzce University Medical School, Department of Infectious Diseases and Clinic Microbiology, 81100 Düzce, Turkey.

<sup>5</sup>Dicle University Medical School, Department of Infectious Diseases and Clinic Microbiology, 21280 Diyarbakir, Turkey.

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## Correspondence to:

Dr. Mehmet Uluğ  
 Özel BSK Anadolu Hastanesi,  
 Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği  
 Alipaşa Mah. FSM Bulvarı  
 No: 9, 43100 Kütahya.  
 Mobile phone: (0532) 4475756, Fax: 0274 2244433 (Hospital)  
 E-mail: mehmetulug21@yahoo.com

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ticular abscess, and seminal vasculitis have been attributed to brucellosis. The most frequent genitourinary complication of brucellosis is EO, affecting 2-20% of males with brucellosis,<sup>10-12</sup> and it was first described by Hardy as a cause of granulomatous orchitis in 1928.<sup>13,14</sup> The testes or epididymis is infiltrated with lymphocytes and plasma cells, and there is an atrophy of the seminiferous tubules.<sup>8</sup> Although the prognosis of brucellar epididymo-orchitis (BEO) is usually good, delay in diagnosis or inappropriate management may result in serious complications, such as testicular abscess, which may require orchiectomy.<sup>10</sup>

In the present study, the clinical characteristics, treatment, and final outcomes of 27 patients with BEO are presented and compared with male patients without EO.

## MATERIAL AND METHODS

This study was retrospectively carried out at Dicle University Medical Faculty Hospital, Department of Infectious Disease and Clinic Microbiology, between January 1998 and December 2006. Our hospital is the largest (1090 beds) in the city of Diyarbakir in the southeastern Anatolia region of Turkey.

Definitive diagnosis of brucellosis was made by isolation of *Brucella* spp. from blood cultures. In the absence of positive blood culture, presumptive diagnosis was made serologically by positive serum standard tube agglutination test together with compatible clinical signs and symptoms of brucellosis, such as fever, sweating, arthralgia, hepatomegaly, and splenomegaly.<sup>8</sup> Among these patients with brucellosis, the diagnosis of epididymitis or EO was based on clinical symptoms (scrotal enlargement, swelling, pain or tenderness not due to other causes), and ultrasonographic examination.

Significant titers were determined to be a Wright's agglutination  $\geq 1/160$ . The following protocol was followed for blood cultures. Two samples of blood (10 mL each) were inoculated into BACTEC bottles and incubated in the non-radiometric semiautomatic BACTEC 9240 system (Becton-Dickinson, Diagnostic Instrument Systems, USA) for 30 days. When a positive bottle was detected, a Gram stain of the broth was performed, and a portion of the fluid was cultured again onto 5% sheep blood, brucella and eosin-methylene blue agar. These subcultures were incubated at 37° C in 5% CO<sub>2</sub> atmosphere for 24-72 hours. Smears from colonies that grew were stained with Gram stain. The isolates of Gram-negative coccobacilli were identified with use of conventional biochemical tests (e.g., motility; oxidase, catalase, and urease tests; effect to glucose and production of H<sub>2</sub>S), and Sceptor system (Becton-Dickinson, Maryland, USA).

Mumps, testicular malignancies, and other bacterial infections were excluded by: absence of history of parotitis, genitourinary tract disease and manipulation, urethral discharge, and sexual exposure; normal serum amy-

lase, lipase, alpha-fetoprotein and beta human chorionic gonadotropin levels and negative scrotal ultrasonographic findings compatible with testis tumor.

Based on the systemic disease duration from the beginning to admission to hospital, patients were classified as acute (less than two months), subacute (2-12 months) and chronic (>12 months).<sup>16</sup> Age, duration of symptoms at admission, history of ingestion of raw milk or milk products, clinical symptoms, results of physical examination, laboratory results, antibiotics administered, and the duration of treatment were recorded. In addition, white blood cell count (WBC), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), C-reactive protein (CRP), blood chemistry profile, and urine analysis were performed in all patients.

Several approaches were used for treatment in these patients: Tetracycline (500 mg/6h PO) or doxycycline (100 mg/12h PO) for 45 days plus streptomycin 1g/day IM) for the first 21 days. Doxycycline (100 mg/12h PO) plus rifampicin (15 mg/kg PO) for 45 days. We used both of them in treatment of our patients.

Patients were followed up fortnightly until the end of the treatment period, monthly for three months, and thereafter every three months for one year. Relapse was assessed by a recurrence of symptoms and signs of the disease, a positive blood culture or rising antibody titer after treatment, in the absence of re-exposure to infection.

Data obtained were analyzed using the Statistical Package for the Social Science (SPSS) for Windows, version 11.0 software (SPSS, Chicago, IL, USA). Student's t-test was applied for comparison of means and chi-square test for comparison of proportions. A p value of < 0.05 was accepted as significant.

## RESULTS

In this study, 302 patients with brucellosis (159 female, 143 male) were analyzed, 27 of them had EO, giving an incidence of EO among males with brucellosis of 18.8%. The clinical characteristics, treatment, and final outcomes of 27 patients with BEO are compared with male patients without EO (n = 116). The mean age of patients with BEO and without EO was 28 ± 8 years (range, 16-46) and 36 ± 14 years (range, 17-74), respectively. This was statistically significant (p = 0.005). Of the 27 patients with BEO, 51.7% lived in rural areas and 48.3% were of urban origin.

An epidemiologic and clinical characteristic of patients with and without EO is shown in Table 1. The presumable infection source could be identified in 78% of patients with BEO and 84% of patients without EO. The possible source of infection was that the patients had consumed unpasteurized dairy products, especially raw milk and fresh cheese, and had direct contact with animals or working with animal products obtained from either sheep or goats.

**Table 1. Epidemiologic and clinical characteristics of patients with and without BEO**

Variable	Patients with BEO (n = 27) n (%)	Patients without BEO (n = 116) n (%)	p value
Mean age (year) ± SD	28.26 ± 8.42	36.39 ± 14.24	0.005
Clinical type			0.285
Acute	22 (81.8)	77 (66.4)	
Subacute	4 (14.8)	27 (23.2)	
Chronic	1 (3.7)	12 (10.4)	
Mean admission time (day) ± SD	11.78 ± 7.28	10.23 ± 5.89	0.244
History			
Ingesting raw milk/ Fresh cheese	21 (77.7)	90 (77.5)	0.983
Ingesting raw meat balls	4 (14.8)	26 (22.4)	0.382
Animal contact	2 (7.4)	20 (17.2)	0.202
Family history brucellosis	2 (7.4)	14 (12)	0.489
Laboratory workers	0	3 (2.5)	0.398
Unknown transmission	6 (22.2)	18(15.5)	0.401
Symptoms			
Abdominal pain	25 (92.5)	14 (12)	< 0.0001
Fever	24 (88.8)	102 (87.9)	0.890
Malaise/ Weakness	22 (81.4)	78 (67.2)	0.146
Arthralgia	20 (74)	99 (85.3)	0.158
Myalgia	19 (70.3)	90 (77.5)	0.428
Sweating	19 (70.3)	86 (74.1)	0.690
Lumbar pain	17 (62.9)	88 (75.8)	0.172
Chills	16 (59.2)	84 (72.4)	0.179
Lack of appetite	13 (48.1)	92 (79.3)	0.001
Headache	10 (37)	71 (61.2)	0.022
Vomiting	4 (14.8)	23 (19.8)	0.549
Rash	2 (7.4)	17 (14.6)	0.318
Jaundice	1 (3.7)	17 (14.6)	0.122
Cough	1 (3.7)	18 (15.5)	0.103
Constipation	1 (3.7)	21 (18.1)	0.062
Depression	1 (3.7)	1 (0.8)	0.257
Diarrhea	0	4 (3.4)	0.328
Scrotal pain	27 (100)	0	
Scrotal redness	24 (88.8)	0	
Scrotal swelling	21 (77.7)	0	
Dysuria	6 (22.2)	0	
Frequent urination	2 (7.4)	0	
Haematuria	1 (3.7)	0	
Signs			
Hepatomegaly	6 (22.2)	32 (27.5)	0.570
Splenomegaly	4 (14.8)	28 (24.1)	0.295
Lymphadenopathy	2 (7.4)	13 (11.2)	0.562
Meningitis	0	8 (6.8)	0.160
Pleural effusion	0	5 (4.3)	0.272
Carditis	0	3 (2.5)	0.398
Usage of antibiotic before admission	10 (37)	29 (25)	0.621

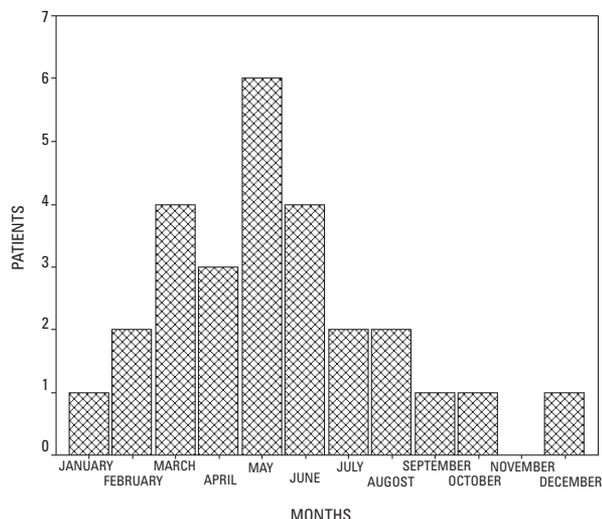
(SD: standard deviation)

No source was identified in six patients (22.2%) with BEO and 18 patients (15.5%) without EO. When the distribution of all cases was examined according to months of the year, an increase was seen in May (Figure 1). There were no significant differences in the distribution of months among any of them.

Of the 27 patients with BEO, the onset of symptoms was acute in 22 patients (81.8%), subacute in four patients (14.8%), and chronic in one patient (3.7%). The mean admission time was  $11.8 \pm 7.3$  days in patients with BEO and  $10.2 \pm 5.9$  days in patients without EO, which is not statistically significant ( $p = 0.244$ ). The symptoms reported at admission are shown in Table 1. None of the patients was asymptomatic. Fever, scrotal pain and swelling, and scrotal redness were the most common symptoms. Headache, lack of appetite, abdominal pain were seen in patients with BEO more than without EO ( $p = 0.022$ ,  $p = 0.001$ ,  $p < 0.0001$  respectively). Urinary symptoms (dysuria, haematuria, frequency or urgency) were seen in six patients (22.2%).

Laboratory findings of patients are shown in Table 2. ESR, WBC, and CRP levels were measured in all patients. ESR ranged from 9-81 mm/h (median, 44 mm/h), 25 patients (92.9%) had ESR  $> 20$  mm/h and two had ESR  $< 20$  mm/h. CRP levels were high (mean  $71 \pm 21.7$  mg/dL; range, 9-140

Figure 1: Distribution of BEO by months of the year.



mg/dL) in 26 patients with BEO. Leukocytosis ( $\geq 10200$  WBCs/mm<sup>3</sup>) was found in 10 patients (37%) and leucopenia ( $< 4600$  WBCs/mm<sup>3</sup>) in two patients (7.4%). Thrombocytopenia ( $< 142000$  platelets/mm<sup>3</sup>) was discovered in six patients (22.2%). Urine analysis was available before

Table 2. Hematological findings of patients with and without BEO

Variable	Patients with BEO (n = 27) n (%)	Patients without BEO (n = 116) n (%)	p value
WBC /mm <sup>3</sup>			$< 0.0001$
<4600	2 (7.4)	22 (19)	
4600-10200	15 (55.6)	84 (72.4)	
10200<	10 (37)	10 (8.6)	
Hematocrit $< 37.7$ g/dL	10 (37)	40 (34.5)	0.802
Platelet $< 142000$	6 (22.2)	26 (22.4)	0.983
ALT $> 45$ IU/L	9 (33.3)	42 (36.2)	0.779
AST $> 45$ IU/L	8 (29.6)	41 (35.3)	0.573
GGT $> 80$ IU/L	4 (14.8)	10 (8.6)	0.329
ALP $> 279$ IU/L	5 (18.5)	23 (19.8)	0.877
Total bilirubin $> 1.2$ mg/dL	8 (29.6)	22 (19)	0.220
Ferritin $> 220$ ng/mL	7 (25.9)	28 (24.1)	0.846
CK $> 226$ IU/L	1 (3.7)	9 (7.8)	0.457
ESR $> 20$ mm/h	25 (92.6)	16 (13.8)	0.368
CRP $> 8$ mg/dL	26 (96.3)	87 (75)	0.014
Positive RF	1 (3.7)	7 (6.3)	0.538
Positive blood culture	10 (37)	42 (36.2)	0.936
Positive urine culture	0	0	

(ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, GGT:  $\gamma$ -glutamyl transpeptidase, CK: creatine kinase, RF: rheumatoid factor)

treatment in all cases; in six, the analysis was abnormal. All patients underwent the Rose-Bengal test; the results were positive for all of them. Also standard tube agglutination testing of initial samples was carried out in all patients and all of them were positive for brucella antibodies (titer,  $\geq 1/160$ ). Two or more blood cultures were drawn under ideal conditions in 17 patients (62.9%). Cultures of blood specimens from 10 (37%) of the 27 patients with EO were positive for *Brucella spp.* and 12 patients with negative blood cultures had received antibiotic therapy previously. Routine urine cultures were taken from all patients in order to rule out other genitourinary infections. No growth was detected in urine cultures.

When we compared clinical and laboratory findings of the patients; young age, high CRP level, and leukocytosis were statistically significant ( $p = 0.005$ ,  $p = 0.014$ ,  $p < 0.0001$  respectively).

Scrotal ultrasonography was performed on all patients. Of the 27 patients, 14 patients (51.8%) had unilateral involvement of testis and epididymis, seven patients had unilateral involvement of testis and only four had unilateral involvement of epididymis. Two patients had bilateral involvement. Testis enlargement was found in 10 patients, and six presented hydrocele. Increased vascularization was detected in 22 patients (81.8%).

All patients received combined antibiotic therapy. Before the diagnosis of BEO, four patients (14.8%) were treated with different antimicrobial treatments. Eight patients (29.6%) had been given antibiotic for brucellosis before admission. Once the diagnosis was correctly established, all the patients were treated for 45 days. Duration of therapy varied according to clinical response and the presence of focal disease. A total of 16 patients (59.2%) received a combination of orally administered doxycycline (200 mg/day) for 6-8 weeks plus streptomycin (1 g/day) for the initial 21 days. Eleven patients (40.8%) received a combination of doxycycline (200 mg/day) plus rifampicin (600-900 mg/day) for 6-8 weeks. There was an improvement in all patients; the fever subsided in 3-7 days, and there was local regression of the scrotal enlargement.

For the 20 patients who were admitted as inpatients, the median duration of hospital stay was  $9.1 \pm 4.2$  (range, 5-21) days; most (17 patients, 62.9%) stayed for 6-10 days and four patients (14.8%) had a hospital stay of  $> 10$  days. Orchiectomy was not required for any of the patients. Relapse occurred in one patient who was discontinuing his therapy.

## DISCUSSION

The incidence of brucellosis has increased during recent years due to the inability to complete its eradication among the animals of Turkey, especially sheep and goats.<sup>4</sup> In our region the most common etiological agent for brucellosis is *B. melitensis*.<sup>17</sup> Our hospital is located in southeastern Anatolia of Turkey, where the majority of the population usually con-

sumes unpasteurized dairy products collected from villages.

Human brucellosis is diagnosed on the basis of epidemiological and clinical findings, and bacteriological and serological tests. Symptoms of the disease may mimic many of the disease and show varied manifestations of acute and chronic infection. Complications of brucellosis sometimes may lead to misdiagnosis.

Genitourinary involvement is rare and EO is one of the manifestations of brucellosis. Brucellosis is a relatively common cause of BEO in geographic areas where *B. melitensis* is endemic.<sup>18</sup> The incidence of BEO is estimated at 2-20%.<sup>10,11,14</sup> In the endemic regions this rate is high,<sup>14,19</sup> Khan *et al.*<sup>20</sup> reported that 35% of the cases of EO in their series were caused by brucellosis. Patil *et al.*<sup>21</sup> reported a rate of 6% and the studies from Turkey reported that the rate was 5.5% and 12.7% in their series, respectively.<sup>18,22</sup> In another study Khan investigated 100 patients with brucellosis and found a rate of 6%.<sup>23</sup> In the present study, EO occurred in 8.9% of all patients and in 18.8% of the male patients with brucellosis. This result was similar to that reported by others.<sup>22-24</sup>

When the distribution of cases according to the months of the year was examined, an increase was seen in the spring and summer months, possibly due to increased consumption of milk and fresh cheese in spring. Several studies have reported a seasonal variation in brucellosis in Turkey.<sup>4,17</sup> As can be seen in Figure 1, of the 27 patients with BEO, 77.7% were seen in spring and summer.

Brucellosis can occur at any age but the most common age group involve adolescents and young adults.<sup>12,17</sup> In the present study, the mean age of patients with EO was 28.2 years and they were significantly younger than the patients without EO, and this was similar with other studies.<sup>11,13,14,20,22</sup> It appears that BEO occurs most commonly in young males. This result clearly shows how the age range reflects the magnitude of the socio-economic and cultural impact of brucellosis in our region and in Turkey.

Most of our patients (81.8%) had an acute brucellosis when EO occurred and this was similar with other studies,<sup>11,13,22</sup> except one.<sup>25</sup> Scrotal pain and swelling, scrotal redness and fever were the most common symptoms and these were similar to the literature.<sup>11,13,20,22,25</sup> Urinary symptoms were seen in 22.2% of our patients, this rate was 31% in Colmenero *et al.*,<sup>2</sup> 47% in Akinci *et al.*,<sup>22</sup> and 69% in Kahn *et al.*<sup>20</sup> studies. On the other hand, the rate was lower in other studies.<sup>10,11,13,25</sup>

Abnormal blood test results are usually mild and non-specific. The hemoglobin level may be lower as a result of prolonged infection, and a moderately elevated ESR is found in most cases. Liver function tests disclose a mild to moderate increase in the hepatic transaminases serum levels.<sup>11</sup> Leukocytosis and high CRP levels are the significant laboratory findings in our study. Leukocytosis has been usually reported as not being a typical feature of brucellosis, but

it was presented as an important feature of BEO in some studies.<sup>20,26</sup> On the other hand, leukocytosis was detected at lower rates in some studies.<sup>10,13,22</sup> High CRP level is also significant in Akinçi *et al.* study.<sup>22</sup> However, as far as we know, no studies have investigated CRP level except this study in the literature.

Since most patients had used antibiotics effective on brucella infection before they were admitted to our hospital, the rate of isolation of microorganism from blood culture was found to be low. Only 37% of our patients had positive culture for *Brucella spp.*, mostly being *B. melitensis*. This rate was similar to Yurdakul *et al.*<sup>10</sup> study, but lower than the other studies.<sup>2,11,22,24</sup>

This study was not designed to analyze the ultrasound features of BEO but ultrasonography plays an important role in the diagnosis, assessment, and management of patients.<sup>26</sup> It is useful to enable the exclusion of the possibility of abscess or tumor before establishing the primary clinical diagnosis. Unilateral EO is the most common genitourinary complication of brucellosis. Infection that is limited to the testis is rare; the epididymis is usually involved in patients who have acute inflammation. Of the 27 patients, 92.5% had unilateral involvement and most of them had EO. This result were compatible with the literature.<sup>11,13,14,20,22,27,28</sup>

The percentage of therapeutic failure or relapse ranges from 0% to 40%<sup>10,11,13,20</sup> and the need for orchiectomy from 0% to 5.1%.<sup>10,11,13,24</sup> The overall percentage of therapeutic failure or relapse in the present study was 3.7%, with no patient requiring surgery. Our results were similar to the literature. On the other hand, we did not find significant differences in the rate of therapeutic failure or relapse between the patients treated with doxycycline plus streptomycin and those treated with doxycycline plus rifampicin, as in the other studies.<sup>2,11</sup>

## CONCLUSION

The frequency of brucella complications is variable in different age groups in Turkey. The most frequent complication of brucellosis is osteoarticular, followed by cutaneous, genitourinary, nervous, and other complications. Brucellosis must be considered as a cause of orchitis in especially endemic regions like Turkey. Unilateral EO is the most common genitourinary complication and most of the cases occur between the second and third decade. Headache, lack of appetite, abdominal pain, leukocytosis and high CRP levels are the significant findings. All patients respond to medical management very well.

Since brucellosis is a preventable disease, knowledge and early diagnosis of the complications are especially important. Therefore, population education and medical precautions are necessary to prevent the harmful effects of brucella and its complications. In addition, primary health care physicians in endemic regions must recognize

that brucellosis is an infection which may involve almost any organ system and which may vary markedly in its clinical presentation.

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