

# BRUCELLOSIS: A RETROSPECTIVE EVALUATION OF 523 BRUCELLOSIS CASES FROM WESTERN ANATOLIA, TURKEY

Nesrin Türker,<sup>1</sup> Bahar Örmən,<sup>1</sup> Nurbanu Sezak,<sup>1</sup> Sevinç Arslan,<sup>1</sup> Hülya Ellidokuz,<sup>2</sup> Figen Kaptan,<sup>1</sup> Sibel El,<sup>1</sup> Serap Ural,<sup>1</sup> İlknur Vardar<sup>1</sup>

<sup>1</sup> İzmir Katip Çelebi University Atatürk Training and Research Hospital, Department of Infectious Diseases and Clinical Microbiology, İzmir

<sup>2</sup> İzmir Dokuz Eylül University Department of Biostatistics and Medical Informatics, İzmir

## ABSTRACT

**Objective:** We investigated epidemiological and clinical features of brucellosis within a period of 16 years in Western Anatolia of Turkey which is a moderately endemic area of the disease. We aimed to clarify our future clinical approach for new cases by observing changes in years.

**Material and Method :** We evaluated brucellosis cases retrospectively which were followed from 1997 to 2012 in our hospital. Our hospital is a regional hospital with a 1100-bed capacity and serves a population of nearly 4,000,000 people in a province located in the Western Turkey. Cases were divided into four equal groups based on follow up years to evaluate epidemiological and clinical features as well as concomitant complications.

**Results:** Totally 523 brucellosis cases were evaluated. Patients within the productive ages were affected the most.

Consumption of unpasteurized milk and milk products was the most common route for transmission. The most commonly identified clinical finding was fever (51.6%). Brucella standard agglutination test was positive in 94.3% of the cases.

Brucella spp was recovered from blood cultures in 22.4% of the cases. Osteoarticular system (29%) was the most commonly involved system. Increased in both the rate of osteoarticular involvement and usage of a combination of three antibiotics was found in recent years.

**Conclusion:** Clinical presentation of brucellosis has changed over time and the most prominent finding was the increase in the ratio of focal organ involvements.

**Keywords:** Brucellosis, epidemiological findings, clinical characteristics, complications *Nobel Med 2014; 10(3): 18-23*

## BRUSELLOZ: TÜRKİYE'NİN BATI ANADOLU BÖLGESİNDE 523 BRUSELLOZ OLGUSUNUN RETROSPEKTİF OLARAK DEĞERLENDİRİLMESİ

### ÖZET

**Amaç:** Brusellozun orta düzeyde endemik olduğu Türkiye'nin Batı Anadolu bölgesinde 16 yıllık süreçte izlenen bruselloz olgularının epidemiyolojik ve klinik özelliklerini araştırdık. Yıllar içerisinde gözlenen değişimleri irdeleyerek gelecekte bruselloz olgularına yaklaşımımızın belirlenmesini amaçladık.

**Materyal ve Metod :** Hastanemizde 1997-2012 yılları arasında izlenen bruselloz olguları retrospektif olarak değerlendirildi. Hastanemiz Türkiye'nin batısında yaklaşık 4.000.000 nüfusa hizmet veren 1100 yatak kapasiteli bir bölge hastanesidir. Olgular epidemiyolojik ve klinik özellikleri ile birlikte eşlik eden komplikasyonları de-

ğerlendirmek üzere izlem yıllarına göre dört eşit gruba bölünerek incelendi.

**Bulgular:** Toplam 523 bruselloz olgusu değerlendirildi. Üretken yaş grubunda olan hastaların en fazla etkilendiği gözlemlendi. En sık tespit edilen bulaş yolu pastörize olmayan süt ve süt ürünleri tüketimi idi. En fazla görülen klinik bulgu ateş (%51,6) idi. Olguların %94,3'ünde brusella STA ( $\geq 1/160$ ) testi pozitif idi. *Brucella* spp, olguların ancak %22,4'ünde kan kültüründe izole edildi. En sık osteoartiküler sistem (%29) tutulumu görüldü. Son yıllarda hem osteoartiküler sistem tutulum oranlarında yükselme hem de üçlü tedavi kullanımlarında artış olduğu bulundu.

**Sonuç:** Zaman içinde brusellozun klinik bulguları değişmiştir ve göze çarpan en önemli bulgu fokal organ tutulum oranlarındaki artıştır.

**Anahtar Kelimeler:** Bruselloz, epidemiyolojik bulgular, klinik özellikler, komplikasyonlar *Nobel Med* 2014; 10(3): 18-23

### INTRODUCTION

Brucellosis is one of the most common infections, with more than 500,000 new cases reported annually worldwide.<sup>1</sup>

In the last decade, although the seroprevalence of the disease in Turkey initially showed an increase between 2001 and 2004, it was followed by a decrease since 2005.<sup>2</sup> More than half of the brucellosis cases in Turkey are from Eastern Anatolia while a substantial number of cases has also been reported from Western Anatolia.<sup>3</sup> The aim of the study was to identify the changes in the epidemiological and clinical features of the disease within a period of 16 years in the Western Anatolia of Turkey, which is a moderately endemic area of the disease and to clarify our future clinical approach for new cases.

### MATERIAL AND METHOD

#### Hospital setting

Our hospital is a regional hospital with a 1100-bed capacity, and serves a population of nearly 4,000,000 people in a province located in the Western Turkey. Annually, 22.500 outpatients and 765 hospitalized patients are seen in the Clinic of Infectious Diseases.

#### Patients

A total of 523 brucellosis cases followed in our department between 1997 and 2012 were

retrospectively evaluated. The hospital database and clinical records were used for analysis. We have received ethical committee approval (Ethics Committee of Dokuz Eylül University, date: 21.06.2012, number: 679-GOA, 2012/22-13) for the use of patient data for publication purposes. Newly diagnosed brucellosis cases 17 years of age or older were included in the study, while relapsed cases were excluded. Cases followed during 16 years were divided into four groups based on follow up years including 1997-2000 (Group I), 2001-2004 (Group II), 2005-2008 (Group III) and 2009-2012 (Group IV) to evaluate the changes in the epidemiological and clinical features as well as concomitant complications.

Brucellosis was diagnosed on the basis of one of the following criteria: isolation of *Brucella* spp from blood cultures, bone marrow, cerebrospinal fluid (CSF) and other body fluid or tissue sample; a compatible clinical picture, supported by the detection of specific antibodies at significant titers and/or the demonstration of an at least four-fold rise in antibody titer in serum specimens taken over 2 to 3 weeks.<sup>1,2</sup> Significant titers were those determined to be  $\geq 1/160$  in the standard tube agglutination test (SAT). *Brucella abortus* S99 antigen (Pendik Veterinary Control and Research Institute, Istanbul, Turkey) was used in SAT. Blood culture specimens were analyzed using BACTEC 9240 (Becton-Dickson Diagnostic Instrument System, Franklin Lakes, NJ, USA) automated culture identification system. Complications were diagnosed according →

**Table 1:** Demographic characteristics of 523 brucellosis cases and routes of transmission with respect to groups

	Group I (n=120)	Group II (n=104)	Group III (n=145)	Group IV (n=154)
<b>Gender</b>	<b>n (%)</b>			
Male	48 (40.0)	56 (53.8)	85 (58.6)	81 (52.6)
Female	72 (60.0)	48 (46.2)	60 (41.4)	73 (47.4)
	<b>Mean (SD)</b>			
Age (years)	48.0 (18.1)	43.4 (15.7)	47.1 (17.4)	47.5 (18.5)
	<b>n (%)</b>			
Consumption of unpasteurized milk and milk products	48 (40.0)	22 (21.0)	64 (44.2)	76 (49.4)
Livestock husbandry practice	32 (26.7)	31 (30.0)	30 (20.7)	48 (31.2)
Unidentified	40 (33.3)	51 (49.0)	51 (35.1)	30 (19.4)

**Table 2:** Clinical and laboratory findings of 523 brucellosis cases according to follow up groups

Clinical findings	Group I (n=120) n (%)	Group II (n=104) n (%)	Group III (n=145) n (%)	Group IV (n=154) n (%)	p value*
Fever	78 (65.0)	64 (61.5)	65 (44.8)	63 (41.2)	<0.001
Hepatomegaly	58 (48.3)	24 (23.1)	33 (22.8)	31 (20.2)	<0.001
Splenomegaly	16 (13.3)	18 (17.3)	24 (16.6)	25 (16.3)	0.848
Lymphadenopathy	6 (5.0)	7 (6.7)	1 (0.7)	5 (3.2)	0.067
Meningeal irritation findings	3 (2.5)	1 (0.9)	3 (2.1)	9 (5.9)	0.103
Cardiac murmur	2 (1.6)	2 (1.9)	6 (4.1)	9 (5.9)	0.216
Testicular edema	1 (2.1)	4 (7.1)	3 (3.5)	6 (7.4)	0.446
Pulmonary findings	0 (0.0)	3 (2.9)	5 (3.4)	10 (6.5)	0.033
Skin rash	0 (0.0)	0 (0.0)	1 (0.7)	4 (2.6)	0.083
<b>Laboratory findings</b>					
Anemia	18 (15.0)	44 (42.3)	46 (31.7)	54 (35.5)	<0.001
Leukopenia	16 (13.3)	17 (16.3)	20 (13.8)	23 (15.1)	0.919
Thrombocytopenia	6 (5.0)	18 (17.3)	17 (11.7)	16 (10.5)	0.031
ESR elevation	80 (66.6)	70 (67.3)	73 (50.3)	99 (64.3)	0.011
CRP elevation	- <sup>a</sup>	16 (15.4)	68 (46.9)	73 (47.4)	<0.001
ALT / AST elevation	60 (50.0)	64 (61.5)	30 (20.7)	55 (36.2)	<0.001
SAT (≥1/160)	120 (100)	92 (88.4)	136 (93.8)	145 (96.0)	0.003
Hemoculture positivity	17 (14.1)	26 (25.0)	24 (16.5)	50 (32.7)	<0.001

\*:  $\chi^2$  test, **ALT**: alanine aminotransferase, **AST**: aspartate aminotransferase, **SAT**: Standart tube agglutination test, **a**: No data obtained in Group I

to physical examination features, laboratory findings and radiological imaging methods including direct radiography, ultrasonography, computed tomography, magnetic resonance imaging and echocardiography.

Treatment protocols used for the treatment of brucellosis differed with respect to age, concomitant diseases, drug side effects, pregnancy and focal organ involvements. Antibiotic therapy was administered for six weeks to cases without complications and the treatment was extended up to 10 months depending on the clinical improvement in cases with focal organ involvements.

### Statistical analysis

Statistical analysis was made using computer software (SPSS version 15.0, SPSS Inc. Chicago, IL, USA).

Chi-square ( $\chi^2$ ) test was used for the comparison of categorical data and variance analysis for average values for age. Data were expressed as “mean (standard deviation; SD)” and percent (%) where appropriate.  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 523 brucellosis cases within a period of 16 years were evaluated in this study. Males composed 51.6% (n=270) of the study population. In all groups most of the patients were in middle ages. There was no significant difference between groups in terms of mean age (p=0.195). However gender distribution revealed significantly higher percent of females in group 1 (p=0.022). The most common route of transmission was consumption of unpasteurized milk and milk products (n=210, 40%) followed by livestock husbandry practice (n=141, 27%). Unidentified modes of transmission was not included in the statistical analysis. When compared, in groups III and IV consumption of unpasteurized milk and milk products was significantly higher (p=0.017). Results are shown in Table 1.

Overall, the most common clinical finding was fever (n=270, 51.6%) and it was followed by hepatomegaly (n=146, 27.9%) and splenomegaly (n=83, 15.9%). Lymphadenopathy (n=19, 3.6%), cardiac murmur (n=19, 3.6%), pulmonary findings (n=18, 3.4%), meningeal irritation findings (n=16, 3.1%), testicular edema (n=14, 5.2%) and skin rash (n=5, 1%) were found less. As shown in Table 2, when the groups were compared, in groups I and II presence of fever and in group I hepatomegaly was significantly higher.

Brucella SAT was determined to be positive in 94.3% (n=493) of the cases, while blood cultures were positive for Brucella spp only in 22.4% (n=117) of the cases. In the 5.7% of the cases brucellosis was diagnosed only with positive blood cultures. Routine laboratory tests revealed anemia in 31% (n=162), leukopenia in 14.5% (n=76) and thrombocytopenia in 10.9% (n=57) of the cases. High ESR and increased levels of CRP were found in 322 (61.6%) and 157 (39%) cases, respectively. As shown in Table 2, distribution of laboratory findings with respect to follow up groups revealed significantly higher percentage of blood culture positivity in group IV.

Considering organ involvement, osteoarticular system (29%) was the most commonly involved system including spondylodiscitis (n=94, 18%), vertebral abscess (n=24, 4.6%), sacroileitis (n=20, 3.9%) and arthritis (n=13, 2.5%). Pancytopenia (5.4%), orchitis (5.2%) meningitis (3.8%), endocarditis (2.5%) and pneumonia (2.7%) were detected less frequently. Higher ratio of osteoarticular involvement (including spondylodiscitis, vertebral →

abscess, sacroileitis and arthritis) and pneumonia in group IV was statistically significant (Table 3).

A combination of two antibiotics (rifampicin and doxycycline or rifampicin and ciprofloxacin) was used in 63.1% (n=330) of the cases, and combination of three antibiotics (rifampicin and doxycycline and ceftriaxone or rifampicin and doxycycline and streptomycin or rifampicin and doxycycline and ciprofloxacin) was used in 36.5% (n=191) of the cases. In two pregnant patients mono therapy with a third generation cephalosporin was used. Treatment with a combination of three antibiotics was preferred in patients with focal organ involvements and all of the cases with osteoarticular involvement (n=151) received this protocol for 3 to 10 months. In two cases with vertebral abscess surgical drainage was performed. In cases with meningitis (n=20) duration of antibiotic treatment ranged from 2 to 4 months. The cases with endocarditis (n=13) also received combination of three antibiotics for 3 to 6 months and two of them underwent valve replacement operation. Seven of the 14 cases with orchitis received a combination of three antibiotics for 2 to 3 months. Overall, mortality was low and one patient who underwent mitral valve replacement operation died. In group IV, usage of a combination of three antibiotics was significantly higher and consequently usage of a combination of two antibiotics was significantly lower when compared with other groups (p<0.001). Change in the frequency of osteoarticular involvement and administration of a combination of two or three antibiotics within years are shown in Figure.

## DISCUSSION

Brucellosis is still an important public health problem in the 21st century in Turkey.<sup>3</sup> The increase in the number of cases from 224 within the first 8 years of follow up (1997-2004) to 299 in the last 8 years (2005-2012) in this study indicates that brucellosis continues to be an important health problem in our region.

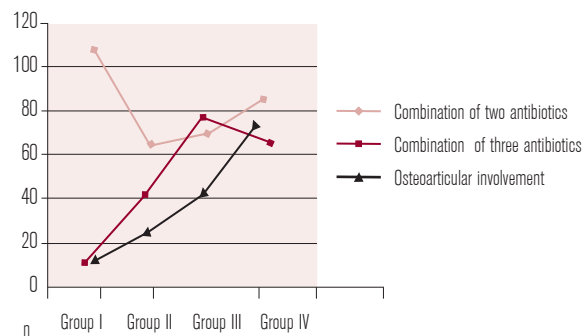
Brucellosis affects young and middle-aged adults in studies from other countries as well as from Turkey, and it is considered a significant cause of morbidity with substantial socioeconomic loss for people in the most productive age groups.<sup>4-7</sup> Likewise, our cases were determined to be in the middle age group.

In countries with low incidence of brucellosis, the disease occurs more commonly among males due to occupational risk, while no gender difference was reported in countries where brucellosis is

**Table 3:** Organ involvements of 523 brucellosis cases according to follow up groups

Organ involvements	Group I (n=120)	Group II (n=104)	Group III (n=145)	Group IV (n=154)	p value*
Spondylodiscitis	10 (8.3)	18 (17.3)	28 (19.3)	38 (24.7)	0.005
Vertebral abscess	0 (0.0)	4 (3.8)	8 (5.5)	12 (7.9)	0.020
Sacroileitis	0 (0.0)	2 (1.9)	5 (3.4)	13 (8.5)	0.002
Arthritis	0 (0.0)	0 (0.0)	1 (0.7)	12 (7.8)	<0.001
Pancytopenia	6 (5.0)	8 (7.6)	9 (6.2)	5 (3.3)	0.438
Meningitis	3 (2.5)	1 (0.9)	6 (4.1)	10 (6.6)	0.115
Orchitis	1 (2.1)	4 (7.1)	3 (3.5)	6 (7.4)	0.446
Endocarditis	2 (1.7)	2 (1.9)	3 (2.1)	6 (4.0)	0.607
Pneumonia	0 (0.0)	6 (5.7)	0 (0.0)	8 (5.2)	0.001

\*:  $\chi^2$  test



**Figure:** Administration of a combination of two or three antibiotics in patients with osteoarticular involvement according to follow up groups

endemic.<sup>4-6,8,9</sup> As our region is a moderately endemic area for brucellosis no gender difference was found in our study.

The main route of transmission is the consumption of unpasteurized milk and milk products in countries where brucellosis is endemic and direct contact and inhalation in developed countries whereas the disease is not endemic.<sup>1,3</sup> In line with literature, consumption of unpasteurized milk and milk products was the leading route of transmission in our study population. In a recent study from Turkey which investigated the knowledge of breeders about brucellosis; the adequate level of knowledge about brucellosis, awareness of contagiousity to humans and the risk of consumption of fresh cheese were found 86%, 77%, and 41.5%, respectively.<sup>10</sup> In our study a significantly higher percent of consumption of unpasteurized milk and milk products in groups III and IV indicates that the level of public awareness is still insufficient in our region.

Clinical manifestations in brucellosis vary depending on the organ and system involvement. Data from past studies conducted in different centers in Turkey revealed fever ranging from 28.8% to 97.2%, →

hepatomegaly from 4.6% to 37.6%, splenomegaly from 12.3% to 35%, lymphadenopathy from 2.4% to 7.6%.<sup>6,9,11-15</sup> In a past study from Northern Iran which included 469 adult cases with brucellosis, fever (67%), splenomegaly (5.7%), and epididymo-orchitis (6.2%) were reported as the most common findings.<sup>4</sup> In our study, in parallel to overall data in Turkey the most common symptom was fever and followed by hepatomegaly and splenomegaly. Lower ratio of fever as a clinical finding in groups III and IV in our study seems to indicate more silent clinical course of brucellosis in the later years with a higher likelihood of delay in admission to infectious diseases clinic and timely diagnosis.

Data on brucellosis cases from Turkey indicate positive SAT titers in 96-100% and positive blood cultures in 15.9-68% of the cases and emphasize the decrease in the ratio of isolation of bacteria with past history of antibiotic treatment.<sup>9,12,14,15</sup> In recent years, automated blood culture systems have been reported to enable faster detection of *Brucella* bacteria.<sup>16</sup> In a study conducted with 84 brucellosis cases in Saudi Arabia, SAT positivity was reported in 95% and blood culture positivity in 37% of patients.<sup>5</sup> In another study from Iran, the ratio for isolation of *Brucella* bacteria from clinical samples was reported to be 2.05% and this low ratio was associated with inclusion of hospitalized patients, past history of antibiotic treatment and inappropriate timing and method of culture sampling.<sup>17</sup> In our study, increased ratio of blood culture positivity in group IV seems to be linked to the accurate timing (before antibiotics were given) and automated methods of blood cultures in recent years.

Osteoarticular system is one of the most commonly involved system in brucellosis. Data from several studies conducted in Turkey indicated that the ratio of osteoarticular system involvement ranged from 25.3 to 69%.<sup>6,9,11,12,15</sup> In a review of the literature on brucellosis cases between 1990-2009 in Turkey, the most frequent involvement was osteoarticular system (43.7%).<sup>18</sup> Based on the data about osteoarticular system involvement of brucellosis in Turkey, spondylitis and sacroiliac joint involvement were the most common involvements.<sup>6,9,11,14,15,19</sup> In our study spondylodiscitis (29%) was the most common osteoarticular involvement and it was followed by vertebral abscess and sacroileitis in decreasing order. Increased ratio of osteoarticular system involvement (spondylodiscitis, vertebral abscess, sacroileitis, arthritis) and pneumonia in group IV was notable. This trend possibly reflects the improved clinical recognition and diagnosis of complications rather than a real increase in complications. The limited

diagnostic capacity in earlier years in our hospital may have prevented the accurate detection of these complications. Alternatively, this trend may indicate changing patterns of access to medical care. The actual cause of complications with brucellosis is unknown, but host susceptibility factors, bacterial strain, route of exposure and delayed treatment may all contribute to it. The duration of infection before treatment may have changed over time, as increasing access to other clinics rather than infectious diseases clinics may have led to increased rates of complications.

The selection of appropriate type and duration of antimicrobial regimen in brucellosis should be made according to presence of focal organ involvement and should be individualized (i.e. pregnancy, age, renal failure). Long term treatment with a combination of three antibiotics has been reported to improve clinical response and to prevent relapse in cases with focal organ involvement.<sup>20,21</sup> Increased percentage of osteoarticular involvement and increased usage of a combination of three antibiotics for treatment was found in groups III and IV in our study population.

In conclusion, brucellosis is still an endemic disease in our region, particularly in the most productive age groups, and this condition seems to pose a threat in terms of socioeconomic loss. In recent years, due to the initial admission of patients to other clinics rather than to the infectious diseases clinics, with the symptoms of focal organ involvements but without accompanying fever, which is a major clinical symptom of brucellosis, might be the cause of delay in accurate diagnosis and administration of inappropriate treatment regimens to the patients. Our findings emphasize that in future more clinically silent brucellosis cases with focal organ involvements necessitating longer duration of treatment might be seen. Effective control of the disease primarily in animals via collaborations between Ministry of Health and Ministry of Food, Agriculture and Livestock as well as increasing public awareness about the disease with behavioral changes especially in people practicing livestock husbandry seem necessary to prevent occurrence of new cases.

The finding of this study should be evaluated within its limitations. It was a retrospective study and follow-up records of all patients could not be found. However the large number of patients in the study and the evaluation of the patients in a single center enabled us to see the changes in epidemiological and clinical features of the disease.

\* The authors declare that there are no conflicts of interest.



## REFERENCES

1. Young EJ. Brucella species. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 7th ed. Philadelphia, PA, USA: Churchill Livingstone, 2010, pp. 2921-2926
2. Erbaydar T, Serpen A, Kurt AÖ. Zoonozlar. In: Ertem M, İnandı T, Can G, Ergör A, Şaşmaz CT, Ayođlu F, Kaya M, editors. Halk Sađlıđı Uzmanları Derneđi Türkiye Sađlık Raporu. Türkiye ISBN:978-975-97836-2-4; 2012. Pp. 84-107.
3. Yuce A, Alp Cavus S. Brucellosis in Turkey. A review. Turk Klimik Journal 2006; 19: 87-97.
4. HasanjaniRoushan MR, Mohrez M, SmailnejadGangi SM, et al. Epidemiological features and clinical manifestations in 469 adult patients with brucellosis in Babol, Northern Iran. Epidemiol Infect 2004; 132: 1109-1114.
5. Bukharie HA. Clinical features, complications and treatment outcome of Brucella infection: Ten years' experience in an endemic Area. Trop J Pharm Res 2009; 8: 303-310.
6. Kurtaran B, Candevir A, Inal AS, et al. Clinical appearance of brucellosis in adults: fourteen years of Experience. Turkish J Med Sci 2012; 42: 497-505.
7. Saçar S, Hırçın Cenger D, Toprak S, Demir M, Turgut H. A clinical evaluation of 30 cases of brucellosis. Turkish Journal of Infection 2008; 22: 11-14.
8. Akhvediani T, Clark DV, Chubabria G, Zenaishvili O, Hepburn MJ. The changing pattern of human brucellosis: clinical manifestations, epidemiology, and treatment outcomes over three decades in Georgia. BMC Infect Dis 2010; 10: 346.
9. Mermut G, Özgenç O, Avcı M, et al. Clinical, diagnostic and therapeutic approaches to complications of brucellosis: An experience of 12 years. Med Princ and Pract 2012; 21: 46-50.
10. Özcan H, Şahin M. Size of business by farmers, brucella disease knowledge levels. Gümüşhane University Journal of Health Sciences 2012; 1: 211-224.
11. Ertek M, Yazgı H, Kadanalı A, Özden K, Taşyaran MA. Complications of Brucella infection among adults: An 18-year retrospective evaluation. Turkish J Med Sci 2006; 36: 377-381.
12. BuzganT, Karahocagil MK, Irmak H, et al. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis 2010; 14: 469-478.
13. Taşbakan MI, Yamazhan T, Gökengin D, et al. Brucellosis: a retrospective evaluation. Trop Doct 2003; 33: 151-153.
14. Demirođlu YZ, Turunc T, Alıřkan H, Çolakođlu Ş, Arslan H. Brucellosis: retrospective evaluation of clinical laboratory and epidemiological characteristics of 151 cases. Microbiol Bul 2007; 41: 517-527.
15. Aydoslu B, Çelik AD, Kulođlu F, et al. Evaluation of brucellosis patients in Trakya University hospital. Microbiol Bul 2006; 40: 257-263.
16. Öztürk R, Mert A, Koçak F, et al. The diagnosis of brucellosis by use of BACTEC 9240 blood culture system. Diagn Microbiol Infect Dis 2002; 44: 133-135.
17. HajjaM, Rahbar M, Keramat F. Epidemiological, clinical, diagnostic and treatment aspects of hospitalized Brucellosis patients in Hamadan. Annals of Tropical Medicine and Public Health 2009; 2: 42-45.
18. Çalık Ş, Gökengin AD. Human brucellosis in Turkey: a review of the literature between 1990 and 2009. Turkish Journal of Medical Sciences 2011; 41: 549-555.
19. Geyik MF, Gür A, Nas K, et al. Musculoskeletal involvement of brucellosis in different age groups: a study of 195 cases. Swiss Med Wkly 2002; 132: 98-105.
20. Solera J. Update on brucellosis: therapeutic challenges. Int J Antimicrob Agents 2010; 36: 18-20.
21. Al-Tawfiq J. Therapeutic options for human brucellosis. Expert Rev Anti Infect Ther 2008; 6: 109-120.