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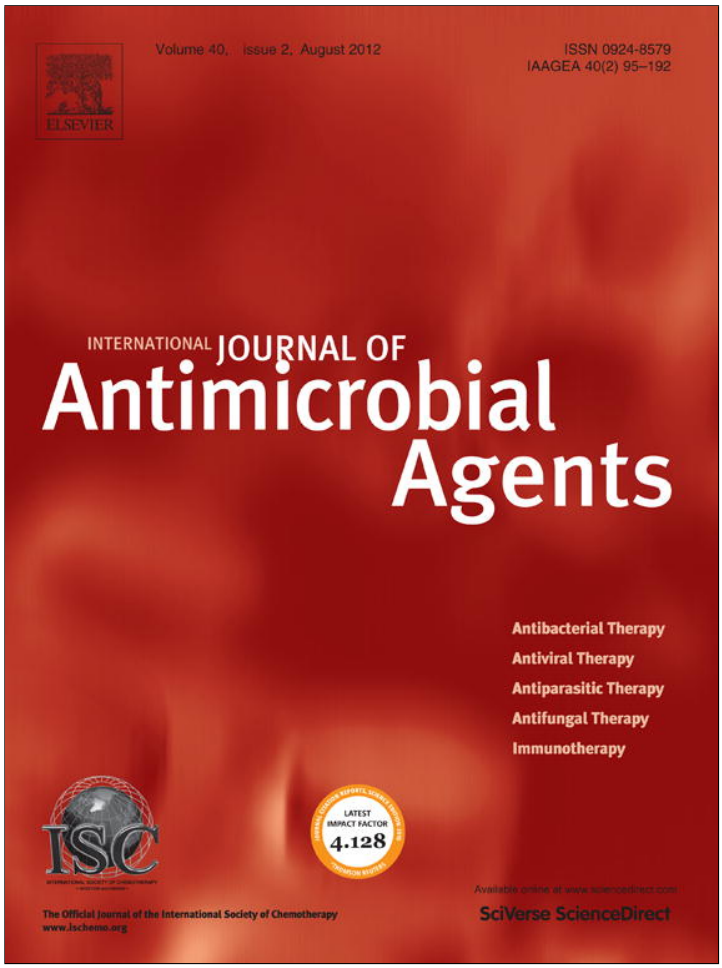

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International Journal of Antimicrobial Agents 40 (2012) 145–150

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Management of *Brucella* endocarditis: results of the Gulhane study

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ARTICLE INFO

Article history:
Received 22 February 2012
Accepted 12 April 2012

Keywords:
Brucellosis
Endocarditis
Therapy
Mortality

ABSTRACT

Brucella endocarditis (BE) is a rare but life-threatening complication of human brucellosis. The aim of this study was to investigate the course of BE along with the therapeutic interrelations. A total of 53 patients with BE hospitalised in 19 health institutions between 2006 and 2011 were included in the Gulhane study. Diagnosis of brucellosis was established by either isolation of *Brucella* sp. or the presence of antibodies, and the definition of endocarditis was made according to Duke's criteria. There were four treatment groups: ceftriaxone combined with oral antibiotics (Group 1); aminoglycosides combined with oral antibiotics (Group 2); oral antibiotic combinations (Group 3); and aminoglycoside plus ceftriaxone combined with an oral antibiotic (Group 4). Involvement rates of the aortic, mitral and tricuspid valves were 49.1%, 43.4% and 5.7%, respectively. Thirty-two patients (60.4%) had an underlying cardiac valvular problem, including previous prosthetic valve replacement ($n = 18$). Medical treatment was provided to 32 patients (60.4%), whilst concordant medical and surgical approaches were provided to 21 patients (39.6%). Mortality in Group 1 was 15% (3/20), whilst in Group 2 it was 5.3% (1/19). In Group 3, 25.0% (3/12) of the cases died, whereas none of the cases in Group 4 died. In conclusion, mortality increased 47-fold with pericardial effusion and 25-fold due to congestive heart failure that developed after BE. Although mortality was lower in the aminoglycoside-containing arm (Groups 2 and 4), statistical analysis could not be performed owing to the small number of patients.

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http://dx.doi.org/10.1016/j.ijantimicag.2012.04.009

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1. Introduction

Human brucellosis, a zoonotic infection, still remains a significant public health problem in areas where *Brucella* infection is endemic among food animals. The disease occurs worldwide; major endemic areas include countries of the Mediterranean basin, the Arabian Gulf, the Indian subcontinent and parts of Mexico, Central and South America [1]. The *Brucella* microbe can infect every tissue, with resultant different clinical presentations. Although death from brucellosis occurs in <1% of cases, the complication most frequently leading to a fatal outcome is infective endocarditis. Hence, *Brucella* endocarditis (BE) is a life-threatening complication of the disease. A meta-analysis evaluating 4204 brucellosis patients derived from 306 local publications reported the rate of endocarditis as 1.2% in Turkey [2].

Unfortunately, there are small case series and case reports in the literature for BE owing to infrequent recognition of the disease. Thus, randomised controlled studies do not exist for BE, and rational therapeutic approaches as well as the course of the disease are unclear. The aim of this study was to investigate the course of BE along with the therapeutic interrelations.

2. Patients and methods

BE patients were included in the Gulhane study. A patient form was sent to participant hospitals and data were collected from 19 centres. Diagnosis of brucellosis was established according to one of the following criteria: (i) isolation of *Brucella* sp. in the blood or any other body fluid or tissue sample; or (ii) the presence of compatible clinical characteristics together with demonstration of specific antibodies at significant titres or seroconversion. Significant titres were considered to be a Wright's seroagglutination $\geq$1/160 or a Coombs' anti-*Brucella* test $\geq$1/160 and an indirect immunofluorescence >1/512 [3]. All patients with suspected BE were examined by transthoracic echocardiography (TTE) and/or transoesophageal echocardiography (TOE), with the definitive clinical diagnosis made in accordance with Duke's criteria [4]. According to the duration of symptoms, BE was classified as acute (<8 weeks), subacute (8–52 weeks) and chronic (>52 weeks) [5]. Four groups were established according to the intravenous antibiotic used:

(i) Group 1: ceftriaxone combined with oral antibiotics;
(ii) Group 2: aminoglycosides combined with oral antibiotics;
(iii) Group 3: oral antibiotic combinations; and
(iv) Group 4: aminoglycoside plus ceftriaxone combined with an oral antibiotic.

2.1. Statistical analysis

The dependent variable of the study was survival with treatment, and the independent variables were clinical course of the disease (acute, subacute or chronic), patient characteristics, mode of transmission of the disease, underlying disorders of the cardiac valves, recovery of the infecting pathogen from blood, bone marrow or vegetation, laboratory findings and complications.

Statistical analysis was performed using SPSS for Windows v.11.5 (SPSS Inc., Chicago, IL). Descriptive statistics were presented as frequency and percent or mean $\pm$ standard deviation and range as appropriate. χ^2 test was used to compare categorical variables. Kolmogorov–Smirnov test was used to evaluate the distribution of variables, and then Mann–Whitney *U*-test was used for comparisons of continuous variables. A *P*-value of <0.05 was considered statistically significant. A logistic regression model was established by the backward stepwise (Wald) method to involve the parameters with significant differences detected by the univariate analyses.

Table 1
Signs and symptoms of 53 patients with *Brucella* endocarditis.

	n	%
Symptom		
Fever	47	88.7
Sweating	28	52.8
Dyspnoea	22	41.5
Palpitation	21	39.6
Sign		
Fever	48	90.6
Cardiac murmur	43	81.1
Spleen enlargement	25	47.2
Liver enlargement	24	45.3
Haematuria	14	26.4
Embolism	8	15.1
Clubbing finger	5	9.4
Proteinuria	4	7.5
Splinter haemorrhages	4	7.5
Petechiae	3	5.7
Osler nodules	2	3.8
Janeway lesions	2	3.8
Retinal haemorrhages	1	1.9

3. Results

In total, 53 patients (19 females and 34 males) were enrolled in this study. The mean age of the patients was 45.3 $\pm$ 14.8 years (range 20–81 years). When the probable modes of transmission were evaluated, 33 (62.3%) had a history of consumption of unpasteurised milk or milk products, 13 (24.5%) were involved with animal husbandry and in 7 (13.2%) the source of transmission could not be established.

Seven cases (13.2%) experienced brucellosis before BE. The mean duration of brucellosis before BE was 9.8 $\pm$ 7.4 months (range 2–24 months). There was an underlying disorder in 40 patients (75.5%). Thirty-two patients (60.4%) had an underlying cardiac valvular problem, including previous prosthetic valve replacement, whereas 21 cases (39.6%) did not have any coexisting valvular disorder. In this study, distribution of previous valvular heart disease was as follows: rheumatic (n = 18); degenerative (n = 11); and congenital valvular disorder (n = 3). In addition, 4 (7.5%) of the patients had hypertension, 3 (5.7%) had chronic renal insufficiency and 1 (1.9%) had cerebrovascular accident. The clinical course of the disease was detected to be acute in 29 cases (54.7%), subacute in 22 cases (41.5%) and chronic in 2 cases (3.8%).

Involvement of the heart valves was as follows: aortic valves, 26 (49.1%); mitral valves, 23 (43.4%); tricuspid valves, 3 (5.7%), and in 1 case (1.9%) both the aortic and mitral valves were affected.

Patients applied to the hospital most frequently with fever, and cardiac murmur was detected to be the predominant sign. Complaints and the physical signs of the disease are presented in Table 1 and laboratory findings of the patients are presented in Table 2. *Brucella melitensis* was isolated in 29 patients (54.7%), whilst the laboratories reported *Brucella* sp. without further identification in 18 cases (34.0%); the infecting agent was not recovered in six cases (11.3%). In all of four cases (100%) with bone marrow cultures and in other 4 of 12 patients (33.3%) vegetation cultures yielded the pathogen. Serological tests used in the diagnosis of BE are shown in Table 3.

In this study, 52 patients had TTE performed, among whom vegetations were detected in 47 (90.4%). Moreover, vegetations were observed by TOE in 40 (95.2%) of 42 patients in whom it was performed. Significant accordance was observed in 41 patients in whom both TOE and TTE was performed (κ = 0.53; P < 0.001). The diameter of the vegetation was 10–20 mm in 30 patients

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Table 2
Laboratory findings of 53 patients with *Brucella* endocarditis.

	Mean	S.D.	Range
Haemoglobin (mg/dL)	10.3	1.8	6.1–15.2
Leukocytes (/mm^3)	6954.9	2804.0	2500–13 100
Platelets (/mm^3)	197 528.3	111 964.7	71 000–548 000
ESR (mm/h)	58.1	26.1	3–140
CRP (mg/dL)	26.79	21.647	3–83
ALT (IU/L)	39.5	37.8	10–258
AST (IU/L)	38.5	28.0	10–154
Creatinine	1.3	1.5	0.4–10.0

S.D., standard deviation; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3
Serological test used in the diagnosis of *Brucella* endocarditis.

Method	Total	Positive [*n* (%)]
Rose Bengal	34	33 (97.1)
STA ≥160	52	49 (94.2)
Coombs ≥160	21	19 (90.5)
Brucella IgM	7	6 (85.7)
Brucella IgG	7	6 (85.7)

STA, standard tube agglutination; Ig, immunoglobulin.

(56.6%), <10 mm in 15 patients (28.3%) and >20 mm in 8 patients (15.1%) according to echocardiography evaluations. Surgery was performed in 3 patients with a vegetation size of <10 mm (20%), 15 patients with a vegetation size of 10–20 mm (50%) and in 3 patients with a vegetation size >20 mm (37.5%). Statistical analysis could not be done to determine the interrelations between the surgical approach and the size of the vegetation owing to the small numbers of patients. Moreover, abscess formation was detected in 4 patients (7.5%), intramural thrombus in 2 patients (3.8%) and fistula formation in 1 patient (1.9%) in echocardiography evaluations. The images were reported to be echolucent in two cases.

3.1. Medical treatment

Medical treatment was provided to 32 patients (60.4%), whilst concordant medical and surgical approaches were provided to 21 cases (39.6%). Various antibiotic protocols (Table 4) were used in the management of the disease. The distribution of cases into treatment arms was as follows: Group 1, $n = 20$; Group 2, $n = 19$; Group 3, $n = 12$; and Group 4, $n = 2$. The mean duration of treatment for all 53 patients was 151.5 ± 61.7 days (range 41–365 days). The mean duration of treatment for patients who underwent surgery was 164.2 ± 80.3 days (range 60–365 days), whilst it was 143.0 ± 45.4 days (range 41–180 days) in those without surgical intervention (Mann–Whitney $U = 297.5$; $P = 0.45$).

Table 4
Antibiotic combinations used in 53 *Brucella* endocarditis patients.

Group	Antibiotic combinations	*n*	%
Group 1	RIF + DOX + CFX	19	35.8
	RIF + DOX + SXT + CFX	1	1.9
Group 2	RIF + DOX + STR	9	17.0
	RIF + DOX + GEN	9	17.0
	RIF + DOX + STR + CIP	1	1.9
Group 3	RIF + DOX + SXT	9	17.0
	RIF + DOX	2	3.8
	DOX + SXT + CIP	1	1.9
Group 4	CFX + STR + RIF	2	3.8
Total		53	100.0

RIF, rifampicin; DOX, doxycycline; CFX, ceftriaxone; SXT, trimethoprim/sulfamethoxazole; STR, streptomycin; GEN, gentamicin; CIP, ciprofloxacin.

The mean duration of antibiotic treatment for those exposed to surgery was found to be 30.5 ± 19.9 days (range 7–92 days) after surgical intervention. The mean durations of parenteral antibiotics were as follows: ceftriaxone, 32.3 ± 22.3 days (14–91 days); streptomycin, 25.3 ± 19.9 days (range 14–91 days); and gentamicin, 27.1 ± 26.5 days (range 11–91 days). There was no significant difference between parenteral antibiotic durations (Kruskal–Wallis $\chi^2 = 0.87$; $P = 0.64$).

After stopping parenteral antibiotics, antibiotics were modified in 10 cases (18.9%) as sequential therapy. Ciprofloxacin was added in three cases and trimethoprim was added in five cases. In one patient, both ciprofloxacin and trimethoprim were given. Finally, trimethoprim/sulfamethoxazole (SXT) was stopped at the second month of treatment and the patient continued with dual oral antibiotics. There was no difference between patients with therapeutic modification and those without ($P > 0.05$).

Mortality in Group 1 was 15% ($n = 3$), whilst in Group 2 it was 5.3% ($n = 1$). In Group 3, which included 12 cases, 25.0% ($n = 3$) died. None of the cases in Group 4 died. Although mortality was lower in Groups 2 and 4 (the aminoglycoside-containing arm), statistical analysis could not be done due to the small number of patients.

3.2. Surgical treatment

Mortality rates according to medical or medical plus surgical therapeutic approaches with respect to valvular involvement are presented in Table 5. Owing to the small number of patients, statistical analysis comparing medical and medical plus surgical therapies could not be done for mortality.

Congestive heart failure (20.8%), uncontrolled infection with antibiotics (17%) and valvular regurgitation were the most frequent indications for surgery. These variables were not found to affect mortality ($P > 0.05$). Moreover, surgical treatment was performed in 47.4% of cases with vegetations ≥10 mm and in 20% of patients with a vegetation size of <10 mm. The difference was not significant statistically ($\chi^2 = 2.32$; $P = 0.12$).

3.3. Outcomes

In this study, 45 patients (84.9%) recovered completely, whilst 1 patient (1.9%) experienced hemiplegia as a persistent sequela. In the peri-treatment period, emboli were shown in various organs in eight patients, congestive heart failure in five, metabolic acidosis in two, spleen abscess in two, cerebral haemorrhage in two, lung oedema in one and hepatic coma in one. Seven cases (13.2%) died in due course of the disease, and death occurred at a mean of 89.1 ± 74.9 days (range 11–240 days). Reasons for death were congestive heart failure in two patients, metabolic acidosis in two patients, hepatic coma in one patient and cerebral emboli in one patient; no reason was identified in one case. There was no cirrhotic background in the patients with hepatic coma. Both hepatic coma and metabolic acidosis were interpreted to be consequences

Table 5
Therapeutic approaches and valvular involvement in 53 patients with *Brucella* endocarditis.

Valvular involvement	Medical		Medical + surgery		Death	
	n	%[a]	*n*	%[a]	*n*	%[b]
Aortic ($n = 26$)	14	53.8	12	46.2	3	42.9
Mitral ($n = 23$)	16	69.6	7	30.4	4	57.1
Tricuspid ($n = 3$)	1	33.3	2	66.7	0	0.0
Aortic plus mitral ($n = 1$)	1	100.0	0	0.0	0	0.0

[a] Row percentage.
[b] Column percentage.

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Table 6
Factors associated with mortality in *Brucella* endocarditis according to the logistic regression model.

	B	*P*-value	OR	95% CI
Pericardial effusion	3.84	0.002	46.60	3.93–551.54
Congestive heart failure	3.20	0.030	24.74	1.37–445.70

OR, odds ratio; CI, confidence interval.

of systemic inflammatory response syndrome by the treating clinicians.

The sex of the patients, mode of transmission, previous history of brucellosis, underlying valvular disease, clinical course of brucellosis (acute, subacute or chronic), and isolation of the infecting agent from the blood, bone marrow or vegetation did not influence mortality ($P > 0.05$). No significant difference existed between patients with previous valvular disorder and those without in terms of mortality (Fisher's exact test, $P = 0.69$). Mortality was 60% in five cases with congestive heart failure and 40% in those without heart failure (Fisher's exact test, $P = 0.013$). Similarly, mortality was higher in two patients with metabolic acidosis (100%) than in those without metabolic acidosis (0%) (Fisher's exact test, $P = 0.015$). Mortality was 62.5% in eight patients with pericardial effusion and 4.4% in the absence of pericardial effusion (Fisher's exact test, $P < 0.001$). Mortality was 66.7% in three patients with chronic renal failure and 10% in those without chronic renal failure (Fisher's exact test, $P = 0.043$). Mortality was 13.2% in patients with vegetation size $\geq$10 mm compared with 13.3% in those with vegetations <10 mm; the difference was statistically insignificant (Fisher's exact test, $P = 1.0$). None of the cases with abscess, thrombus and fistula formations died. The presence or absence of these complications did not affect mortality ($P > 0.05$). There were no significant differences for mortality and surgical intervention between native valve and prosthetic valve endocarditis ($P > 0.05$).

The mean leukocyte count was significantly lower in those who died ($4780.0 \pm 1763.2/mm^3$) compared with survivors ($7285.9 \pm 2796.9/mm^3$) (Mann–Whitney $U = 72.0$; $P = 0.019$). Likewise, platelet counts were lower in mortality cases ($129\,714.2 \pm 64\,373.1/mm^3$) than survivors ($207\,847.8 \pm 114\,496.4\,mm^3$) (Mann–Whitney $U = 85.5$; $P = 0.047$). In contrast, there was no statistical significance for laboratory parameters other than leukocyte and thrombocyte counts between survivors and non-survivors ($P > 0.05$).

Variables affecting mortality were included in the logistic regression model. These parameters were congestive heart failure, metabolic acidosis, chronic renal failure, pericardial effusion, and leukocyte and thrombocyte counts. Finally, mortality increased 46.6-fold with pericardial effusion detected with echocardiography and 24.7-fold due to congestive heart failure seen after BE (Table 6).

4. Discussion

Brucellosis is an endemic disease in Turkey, and 10 000–15 000 human brucellosis cases were reported annually between 2000 and 2005 [6]. Cardiovascular complications of brucellosis include endocarditis, pericarditis and mycotic aneurysms involving the brain, aorta and other vessels. Before effective therapy, including valve replacement surgery, BE was known to be almost always fatal and is still the most feared complication of brucellosis today [2]. According to our data, although the clinical presentation of the disease appears to be indifferent from other forms of endocarditis [7], BE seems to have specific features related to virulence characteristics of the infecting pathogen, and this issue is the primary concern of this paper.

In case of suspicion of brucellosis, establishing the diagnosis is not always easy. Isolation of *Brucella* sp. from a clinical specimen may not be practical in some cases who had previously used antibiotics in addition to the lower efficacy of culture methods. Hence, serological tests have been continuously used in brucellosis-endemic areas [8]. In a report by Reguera et al., blood cultures were positive in 63% of BE patients [9]. In patients in the current study, cultures were as much positive as serological tests, which were effective in ca. 90–95% of cases. This was probably due to the use of sophisticated Bactec™ or BacT/ALERT® blood culture systems in Turkey.

In this study, it appears that although BE develops on valves previously damaged by rheumatic fever or congenitally malformed, it may also occur on previously normal valves. This was noticed in the initial BE case series, and implantation of the *Brucella* strain onto the valvular endocardium may result in excessive destructive lesions [10]. According to the current data, more than one-half of the patients were previously aware of their valvular heart damage. On the other hand, although two-fifths of the patients did not report any underlying valvular disease, the pre-existing damage, probably due to rheumatic heart disease, may have gone unnoticed. Thus, *Brucella* sp. appears to have a predilection to invade damaged endocardial tissue. In a small case series, it appears that BE tended to involve the aortic valve [2]. Accordingly, in the current study one-half of the cases had aortic involvement. On the other hand, mitral valve endocarditis was almost as frequent as aortic infection and was detected in more than two-thirds of the patients. In rheumatic heart disease, the mitral valve is involved in nearly all cases whilst aortic valve involvement is ca. 20–30% [11,12]. Thus, mitral valve involvement should be expected in a substantial proportion of BE patients, depending on the epidemiology of rheumatic fever and heart disease in brucellosis-endemic regions.

According to the World Health Organization (WHO), treatment of endocarditis caused by *Brucella* sp. usually requires a combination of antimicrobial therapy [13,14]. Treatment of BE imposes particular problems owing to the need for maintenance of bactericidal antibiotic concentrations in the valvular vegetations. In addition, delays in making the diagnosis often result in progressive valve damage. For these reasons, both antimicrobial chemotherapy and surgical replacement of the damaged valve are often necessary. In the literature, various antibiotic combinations of different durations have been reported to be used in BE, but in small patient groups [9].

The combination of doxycycline plus an aminoglycoside results in rapid killing of the bacteria, and rifampicin or SXT are used for their ability to penetrate cell membranes [9]. As an example, ceftriaxone-based regimens were found to be more successful and to require shorter therapy than the oral treatment protocol in the management of neurobrucellosis [15]. The probable reason may be the superior accumulation of ceftriaxone in the cerebrospinal fluid. However, the issue of selecting ceftriaxone is somewhat different in BE patients. In a BE case series, ceftriaxone was the drug of parenteral choice in the management of the disease. Most likely reasons for this choice were nephrotoxicity and ototoxicity, which have the frequent potential to be seen in the elderly population related to aminoglycosides. Thus, advanced age of BE patients may facilitate the use of ceftriaxone. A detailed analysis and a meta-analysis evaluated the use of aminoglycosides in the treatment of bacterial endocarditis [16,17]. Use of aminoglycosides in combination with a β-lactam or vancomycin may be of benefit for patients with infective endocarditis (IE) due to Gram-positive bacteria. Data from animal models show somewhat mixed results. There are reports of greater reductions of bacteria within vegetations with thrice-daily compared with once-daily dosing, but other animal model studies demonstrated no difference. There are no controlled clinical trials. At present, it is suggested that once-daily therapy not be employed for the treatment of enterococcal endocarditis [18]. In the current study, although statistical comparisons

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could not be made, aminoglycosides appear to have better efficacy in the management of BE. However, special caution needs to be indicated for the toxicity of this group of antibiotics. In this context, special concern should be mentioned on the combined use of ceftriaxone and aminoglycosides in future BE studies.

Prolonged therapy (8 weeks minimum) is recommended in BE and therapy should be continued for several weeks if surgery is applied. Some reports suggested that SXT, aminoglycosides or ciprofloxacin must be added to the rifampicin and doxycycline regimen and the duration of treatment must be around 6 weeks to 4 months [19,20]. In the current study, patients were treated with antibiotics for a mean duration of 5 months. There was no significant difference in antibiotic duration between patients exposed to surgery and those treated with antibiotics alone, and the former group of patients was given treatment for an additional 1 month on average after surgery. At this point, controversy seems to exist on the duration of antibiotics in the literature and there are case series recommending an additional 6 months of therapy following surgery [21]. However, the current data disclose a more conservative approach for antibiotic treatment in the post-surgical period.

Surgery was not an option in the management of IE until 1961 when Kay et al. excised fungal vegetations from the tricuspid valve of a patient [22]. The most frequent indications during the course of IE are congestive heart failure, refractory sepsis, embolic complications and vegetation size [23]. Thus, valve replacement and even valve repair have become commonplace in the management of selected complications of BE, and a reduction in mortality from BE has been ascribed to the combination of antibiotic therapy and timely surgical intervention [10]. In the patients in the current study the indications for surgery in descending order were congestive heart failure, uncontrolled infection with antibiotics and valvular regurgitation. In the IE guideline, the size of the vegetation is one of the parameters used in decision-making for surgical intervention [24]. Although flexibility is cautiously emphasised, surgical operation is generally recommended for vegetations $\geq$10 mm in size. Even emergent surgical operation is advocated when the vegetation size exceeds 15 mm, which was noted to be a significant contributing factor for mortality [24–26]. In the current study, two-thirds of patients had a vegetation size $\geq$10 mm. Consequently, one-half of the patients with a vegetation size $\geq$10 mm exposed for surgery compared with one-fifth of those with vegetations below that threshold were operated. Thus, the decision of surgery should be carefully individualised for each BE case.

Endocarditis appears to account for most of the 5% total mortality rate of human brucellosis [27]. In-hospital mortality was reported to occur approximately at the start of the second month after hospitalisation during IE [26]. However, in the BE cases in the current study, mortality was observed around the third month of treatment. The probable reasons for late mortality in BE may be the absence of classic virulence factors such as exotoxins or endotoxins in *Brucella* spp. and the atypical pathogenicity of the lipopolysaccharide. Thus, the organism has a low virulence that may extend survival [1]. Other data supporting this hypothesis are that one-third of patients with *Staphylococcus aureus* endocarditis, a highly virulent microorganism, died despite treatment [28], whilst 13% of the patients in the current study died. In the past, mortality in BE was believed to be high [1]. However, optimum interpretation can be that BE appears to result in the major proportion of deaths related to brucellosis, but it is a relatively benign form of IE compared with those due to highly virulent microorganisms.

Heart failure remains the most common cause of death due to IE and is the most frequent reason for surgery in these patients. The usual cause of heart failure is valvular insufficiency resulting from infection-induced damage. Rarely, embolism of the coronary ostium can cause acute myocardial infarction and subsequent heart failure [29]. On the other hand, pericardial effusion leading to cardiac tamponade has been reported in a BE case in the literature [21]. Thus, pericardial effusion and heart failure were independent risk factors for mortality in this study. Consequently, the physical examination of a probable BE patient should include a careful cardiac examination for signs of new regurgitant murmurs, heart failure or signs of pericardial effusion. In this study, fever, sweating, dyspnoea and palpitation were the most frequent symptoms, whilst fever, murmurs, spleen and liver enlargement, and haematuria were the most frequent findings. In addition, the causative microorganism may affect the course of IE and the disease may present as a rapidly progressive infection or may have a subacute or chronic character that may confuse initial clinical assessment [24]. That was the case in the BE patients in this study and approximately one-half of the patients had a subacute or chronic character. That is, the disease has an onset of >2 months in these cases. In the laboratory, BE patients were seen to present with normal or partially increased leukocyte counts and liver transaminases, relatively low haemoglobin levels, and high erythrocyte sedimentation rates and C-reactive protein levels (means of 58 mm/h and 27 mg/dL, respectively).

This is the largest BE patient set in the literature. Since it was nearly impossible to perform a prospective cohort study for such a rare disease, we were forced to carry out a retrospective one. Besides, different antibiotic combinations further limited the comparison of treatment protocols in detail. Although it seems that every parenteral antibiotic has both advantages and disadvantages, aminoglycosides appear to be superior as a part of a combination regimen in those who can tolerate them. In addition, brucellosis should be considered in patients with risks of dietary and occupational exposure in endemic areas. In this context, special concern is indicated for cardiovascular complications of this subtle disease.

Brucellosis is an endemic disease in Turkey. Both people involved with animal husbandry and consumers of milk products are at risk of the disease. Therefore, there is a strong need for collaboration between veterinarians and health staff. Thus, physicians as well as the public are being educated on an ongoing basis for the prevention and control of brucellosis in Turkey today. Brucellosis should be considered in patients with a risk of dietary and occupational exposure in endemic areas. In this context, special concern is indicated for cardiovascular complications of this subtle disease.

Funding: No funding sources.

Competing interests: None declared.

Ethical approval: This study was approved by the Ethics Committee of Harran University Medical Faculty (Sanliurfa, Turkey).

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