

## Native Valve Brucella Endocarditis

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### ABSTRACT

**Objective:** Brucellosis is frequently seen in Mediterranean and Middle East countries, including Turkey. We report the medical and surgical management of 31 cases of native endocarditis.

**Material and Method:** Thirty-one patients were admitted to our clinic with suspected Brucella Endocarditis. The diagnosis was established by either isolation of Brucella species, or the presence of antibodies. Following preoperative antibiotic therapy patients underwent valve replacement with excessive tissue debridement. Patients were followed up with Brucella titers, blood cultures, and echocardiography.

**Results:** On admission all patients were febrile and mostly dyspneic (NYHA Class 3 or 4). The blood tests were normal except for elevated ESR, CRP and serological tests. The aortic valve was involved in 19 patients, mitral valve in 7 patients, and both valves in 5. After serological confirmation of BE, antibiotic therapy was maintained. Twenty-five of the patients received rifampicine, doxycycline, and cotrimoxazole; 2 of them received a combination of rifampicine, streptomycin, and doxycycline; and 4 of them received rifampicine, tetracycline, and cotrimoxazole. Tissue loss in most of the affected leaflets and vegetations were presenting all patients. Valve replacements were performed with mechanical and biologic prostheses. All the patients were afebrile at discharge but received the antibiotics for  $101, 2 \pm 16, 9$  days. The follow-up was  $37, 1 \pm 9, 2$  months.

**Discussion:** In our retrospective study, combination of adequate medical and surgical therapy resulted in declined morbidity and mortality rate. The valve replacement with aggressive debridement is the most important part of the treatment, which should be supported with efficient preoperative and long term postoperative medical treatment.

### Introduction

Although Brucellosis is rare in western countries, it is frequently seen in Mediterranean, Middle Eastern, Asian, and South American countries.<sup>1</sup> It is a systemic infectious disease caused by the genus *Brucella*, the gram-negative bacilli. Majority of human brucellosis is caused by *Brucella melitensis*.<sup>2</sup> It is a mild or asymptomatic disease, and multiple organs can be involved. Most commonly osteoarticular system is affected, but genitourinary, central nervous and cardiovascular system can also be involved.<sup>2</sup>

Brucella endocarditis (BE) is rare (the incidence is 1–2% in all over the world), however it is the main cause of the

mortality in patients with Brucellosis.<sup>2</sup> The aortic valve is the most commonly involved, which may also lead to aortic root abscess formation.<sup>3</sup>

A patient with a heart murmur who has a history of ingestion of nonpasteurized milk or other animal products or exposure to infected animals must be intensely evaluated in suspicion of brucella endocarditis.<sup>4</sup> The morbidity and mortality associated with BE can be reduced with adequate medical and surgical approach.<sup>5</sup>

We report the management of 31 cases of native BE with combined medical and surgical therapy.

## Material and Methods

Between 1996 and 2007, 18 male and 13 female patients, ranging between 22 and 69 years, with BE were admitted to Ankara University School of Medicine.

## Diagnosis

The diagnosis of brucellosis was established according to two criteria: isolation of *Brucella* species in blood, any other body fluid or tissue sample, or the presence of compatible clinical characteristics together with the demonstration of specific antibodies at significant titers or sero-conversion. Significant titers were considered to be a Wright's seroagglutination  $>1/160$  or a Coombs' anti-*Brucella* test  $>1/320$  and an indirect immunofluorescence  $>1/512$ .<sup>6,7</sup>

Results of *Brucella* standard tube agglutination tests higher than  $1/320$  were accepted as positive. Also consecutive blood cultures were taken from the patients.

All patients with suspected *Brucella* endocarditis were examined by transthoracic (TTE) and transesophageal (TEE) echocardiography, with the definitive clinical diagnosis made in accordance with Duke's criteria, and the diagnosis was confirmed microbiologically or serologically.

## Operative Technique

Patients were operated under general anesthesia with median sternotomy and cardiopulmonary bypass. Following aortic clamping and cardiac arrest with antegrade cardioplegia, the valves (aortic or mitral) were examined by the surgeon, and excessive debridement (debridement of the infected tissue including the uninfected border) with valve excision was performed. The valves were sutured using inverted pledgetted sutures. Following weaning off cardiopulmonary bypass TEE was performed to evaluate the replaced valve and the surrounding tissue.

## Follow up

Patients were examined with TTE at 1<sup>st</sup> and 7<sup>th</sup> postoperative days and discharged with anticoagulant and antibiotic treatment. During the first 6 months patients were followed up in every 6 weeks, thereafter all patients were followed up in every 4 months for a minimum of 24 months. Physical examination, telecardiography, blood counts, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were studied in each visit, also *Brucella* titers, blood cultures, and echocardiography were repeated.

## Statistical Analysis

All data were expressed as the mean  $\pm$  standard deviation. The statistical evaluation of the results has been made according to the *t* test for paired samples.

## Results

The mean age of the patients with BE was  $44.6 \pm 9.3$  years (ranging between 22 and 69 years), and there were 18 male and 13 female (Table I).

Twenty five patients had been exposed to infection with *Brucella* species; 6 patients reported usual or occasional contact with animals whereas 19 of them consumed nonpasteurized dairy products. In six patients there were no contact or consumption of animal products.

On admission all patients were febrile with oral temperature greater than  $38^\circ\text{C}$  and they were mostly in NYHA Class 3 or 4. White blood cell counts were within normal limits in all patients (between 4,000 and 8,800/mm<sup>3</sup>) however all were mildly anemic (Table I). Also ESR (40 to 126 mm/h) and serum CRP (12-27 mg/L) levels were higher in these patients.

Previous cerebral hemorrhagic strokes were present in two patients, additionally two patients had lumbar spondylitis.

Cardiac murmurs were present in all patients, also six had a history of rheumatic fever in childhood. Twenty five patients had signs of congestive heart failure, consistent with hepatomegaly in 6 cases which was confirmed by abdominal ultrasonography. Except for atrial fibrillation in 2 patients, conduction disturbances were not detected (Table I).

The endocarditis involved the aortic valve in 19 patients, the mitral valve in 7, and both heart valves in 5 patients (Figure I-II). Echocardiographic findings are summarized in Table II.

Blood cultures were positive in 14 patients (45%) with *Brucella mellitensis* being isolated in all. The rest of the patients with negative blood cultures had received previous antibiotic therapy. Also all the patients had *Brucella* titers more than  $1/320$  at the time of admission (Table I).

After serological confirmation of BE, antibiotic therapy was maintained. Two of the patients received a combination of rifampicine (900 mg bid), streptomycin (16 mg/kg/24 hours IM), and doxycycline (200 mg/kg bid); twenty five of them received rifampicine, doxycycline (200 mg/kg bid), and cotrimoxazole (15 mg/kg bid); and rifampicine, tetracycline (8 mg/kg tid), and cotrimoxazole was the preferred drugs in 4 patients. After adequate antibiotic therapy patients were operated, mean duration of preoperative antibiotic treatment was  $29, 0 \pm 6, 4$  days.

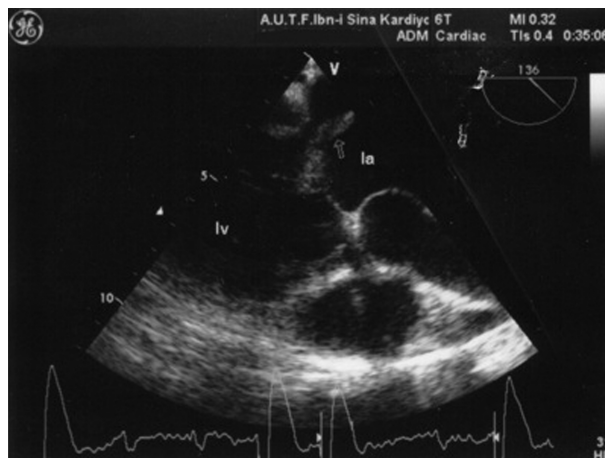
The mean cross clamp and CPB times were  $54, 1 \pm 8, 6$  minutes and  $92, 6 \pm 8, 2$  minutes respectively (Table III). Tissue loss was detected in most of the affected leaflets (Figure III). Vegetations were present in all of the patients; type and severity of valvular lesions are summarized in Table II.

In only ten patients operative valvular cultures were positive, and all were *Brucella melitensis*. These were the ten of the fourteen patients who had positive preoperative blood cultures.

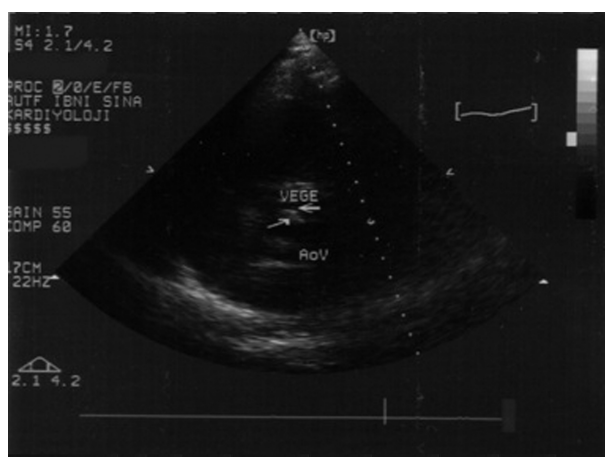
**Table 1.** Preoperative Clinical Data and Laboratory Findings

Variable	Number of Patients (n = 31)
Number of BE patients	31
Mean age (y)	44.6 ± 9.3
Sex ratio (M/F)	18/13
Contamination with the microorganism caused by:	
Direct contact with animals	6
Consumption of non-pasteurized dairy products	19
No contact or consumption of dairy products	6
Diabetes mellitus	6
Hypertension	7
Preoperative MI	1
Embolic events	
Cerebral hemorrhagic stroke	2
Febrile patients	31
NYHA Class	
I	5
II	3
III	13
IV	10
Mean hemoglobin	9.1 ± 1.1
Mean hematocrit	29.4 ± 4.4
Mean white blood cell count/mm <sup>3</sup>	4751 ± 1421
Mean ESR	87.1 ± 11.3
Mean CRP	22.1 ± 4.2
Rheumatic fever history	6
Congestive heart failure	25
Involved valves	
Aortic	19
Mitral	7
Aortic-mitral	5
(+) blood cultures	
Preoperative	14
Operative	10
(+) Serology	31

Abbreviations: BE = *Brucella* endocarditis; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; MI = myocardial infarction; NYHA = New York Heart Association.



**Figure 1.** Preoperative echocardiography of a case with native brucella endocarditis. The arrow indicates a vegetation on the mitral valve (la=left atrium, lv=left ventricle).



**Figure 2.** Vegetation on the aortic valve in a patient with the diagnosis of brucella endocarditis (AoV=aortic valve, Vege=vegetation).

The infected valves were replaced with mechanical prosthesis in 25 patients and bioprosthetic valves in 6 patients. Three of these 6 patients were older than 65 and the remaining three ladies had plans to get pregnant in the future.

The hospital mortality was 6.4% (2 patients). A young female patient experienced a stroke which resulted in death, she had undergone mitral valve replacement with a bioprosthesis, and the other patient died due to prolonged intubation and pneumonia. The mean intensive care unit and hospital stays were similar between groups (Table I).

All the patients were afebrile at discharge. They received a combination of antibiotics for a mean of 101, 2 ± 16, 9 days. The end-point of antibiotic therapy was normalization of *Brucella* agglutination titers (1/160), and clinical evaluation

Table 2. Echocardiographic and Operative Findings

Patient No.	Valve Pathology	Maximum Valve Gradient (mm Hg)	Vegetation	Abscess	Surgical Examination
1	AS + moderate AI	37	+		Large vegetation
2	Severe AI		+		2 small vegetations on the left coronary cusp
3	AS + moderate AI	20	+		Vegetation on the aortic cusps
4	Moderate MI		+		Small vegetation
5	Severe AI		+	+	Big vegetation on the calcified cusps. Abscess formation
6	Severe AI + MS	14	+(both valves)		Laceration on the aortic valve. Vegetations on both valves
7	Moderate AI		+		Big vegetation and calcified aortic cusps
8	AS + severe AI	64	+	+	Abscess formation and small vegetation
9	Severe AI and MI		+(both valves)		2 large vegetations on both the mitral and aortic valves
10	Moderate MI and MS	13	+		Large vegetation on the posterior cusp
11	Severe AS and AI	77	+(noncoronary cusp)		2 small vegetations on the noncoronary cusp
12	Severe AS and MS	64 (aortic) and 19 (mitral)	+(only mitral)	+(aortic wall)	Vegetation on the mitral posterior cusp and abscess formation on the aortic wall
13	Severe AI and MI		+(both valves)		Abscess formation under noncoronary cusp and perforation of mitral anterior cusps. Vegetations on both valves
14	Moderate AI		+	+	Rupture in the non-coronary leaflet and big vegetation on the right coronary cusp
15	Mild MI		+		Large vegetation on the anterior mitral leaflet
16	Severe MI		+		2 small vegetations on both leaflets
17	Severe AI		+		Large vegetation on the right coronary cusp
18	Severe AI		+		2 small vegetations on the left and non-coronary cusps

Table 2. (Continued)

Patient No.	Valve Pathology	Maximum Valve Gradient (mm Hg)	Vegetation	Abscess	Surgical Examination
19	AS + moderate AI	32	+		Vegetation on the right aortic cusp
20	Moderate MI		+		Small vegetation
21	Severe MI		+		Big vegetation covering both leaflets
22	Severe AI + MS	13	+		Vegetations on both valves
23	AS	55	+		Big vegetation and calcified aortic cusps
24	AS + severe AI	65	+	+	Abscess formation and small vegetation
25	Severe MI		+		2 large vegetations on both mitral leaflets
26	Moderate MI and MS	14	+		Large vegetation on the posterior cusp
27	Severe MS	22	+		2 small vegetations on the anterior leaflet
28	Severe AS	77	+	+	Vegetation on the noncoronary cusp and abscess formation on the aortic wall
29	Severe AI		+		Small vegetation on the left coronary cusp
30	Moderate AI		+	+	Large vegetation on the right coronary cusp and aortic valve abscess formation
31	Mild MI		+		Large vegetation on the anterior mitral leaflet

Abbreviations: AI = aortic insufficiency; AS = aortic stenosis; MI = mitral insufficiency; MS = mitral stenosis.

of the patients. Standard tube Brucella agglutination titers presented gradual decrease in all patients within 6 months. All postoperative and follow up blood cultures were negative.

In control echocardiographies, neither vegetations nor paravalvular leaks were detected.

Mean postoperative follow-up time was 37, 1 ± 9, 2 months (ranging between 16 and 125 months).

**Discussion**

In human beings Brucella infections are associated with a high degree of morbidity, 30–40% of cases have focal complications. Focal complications can affect any organ or system, which explains why those affected are not always seen by specialists in infectious diseases, also by other medical specialists.

The incubation period of brucellosis is about 2 to 6 weeks, but it may occasionally be much longer.<sup>4</sup> The main route of infection is usually the intake of nonpasteurized dairy products.<sup>2</sup> Twenty-five of the cases in our study had a history of nonpasteurized dairy product consumption or direct animal contact.

Endocarditis is an uncommon complication of brucellosis. Its incidence varies widely and ranges from 0.7 to 10.9%.<sup>8,9</sup> In a previous study six (1.13%) BE cases have been reported in 530 brucellosis patients.<sup>10</sup> But there are not many reports of native brucella endocarditis in the literature.

Despite its low frequency, endocarditis is a very severe complication of brucellosis, with a higher mortality rate.<sup>2</sup>

Usually the left side of the heart is affected, predominantly the aortic valve (29%). Involvement of endocardium may cause acute valvular regurgitation (aortic

Table 3. Operative and Postoperative Data

	Number of the patients (n = 31)
Hospital mortality	2
Emergency operations	4
Cross clamp time (min)	54.1 ± 8.6
CPB time (min)	92.6 ± 8.2
Postoperative drainage	427 ± 139
IABP requirement	0
Complications	
Arrhythmia	5
Postoperative MI	. . .
Reexploration	1
ICU stay (h)	40.3 ± 8.5
Hospital stay (days)	10.3 ± 4.2

Abbreviations: CPB = cardiopulmonary bypass; IABP = intra-aortic balloon pump; ICU = intensive care unit; MI = myocardial infarction.

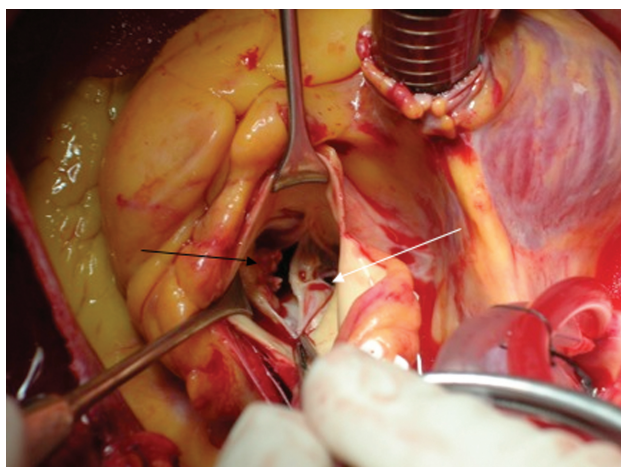


Figure 3. Mobile vegetation on the infected cusp (black arrow), and torn cusp (white arrow).

and/or mitral), arrhythmias (bradycardia), cardiac fistulas, microabscesses within the cusps, calcifications, and commissural degeneration.<sup>11</sup> In our study the aortic valve was involved in 19 patients, and the mitral valve in 7 patients, and in the remaining 5 patients both of the left sided valves were involved. We observed abscess formation in seven patients, and rupture of an aortic cusp was also present in one patient (Figure III).

The incidence of embolism in BE is not usually greater than other types of endocarditis.<sup>12,13</sup> Two patients had experienced embolic events preoperatively which resulted in non-severe sequelae. One of the two hospital deaths was a 31 years-old lady who experienced an acute stroke in the postoperative period.

Heart murmur is a hallmark of all infective endocarditis cases, and also BE. A practitioner must keep two main findings in mind for the diagnosis of BE; fever and cardiac murmur.<sup>14,15</sup>

Even with a high degree of suspicion, the diagnosis of brucellosis is not always easy. Serologic tests, are more sensitive than blood cultures but not specific, and usually difficult to interpret in areas where the disease is endemic. Also serologic tests may be negative during the early stage of the disease. Blood cultures are more specific, however they lack sufficient sensitivity.<sup>16</sup>

Due to the slow growth rate of *Brucella* species and their requirement of a suitable culture medium, BE is often associated with a higher rate of negative blood cultures than other bacterial endocarditis. BE takes place in published reports mainly listed in the section of pathogen-induced endocarditis with negative blood cultures.<sup>17,18</sup> Although all the patients in our study have brucella titers (Wright's agglutination test) more than 1/320 which was accepted as positive, most of the patients were culture negative, only 14 patients (45,16%) were culture positive before the operation, and we consider this as a result of previous antibiotic treatment. In a report by Reguera et al, blood cultures were positive in 63.6% of patients when blood cultures were processed in the absence of previous antibiotic therapy.<sup>4</sup>

*Brucella* species can produce very destructive lesions in the valvular endocardium, it is traditionally believed that the therapeutic approach to *Brucella* endocarditis must involve the combination of both medical and surgical treatment.<sup>4,6,12,13,14</sup> However, this great destructive capacity is probably related more to a delayed diagnosis than to the supposed virulence of the bacteria. Indeed, endocarditis caused by other pathogens provokes similar destructive lesions over a much shorter period of time. Cure of *Brucella* endocarditis with medical treatment alone has been reported occasionally.<sup>19</sup>

Currently, the drugs of choice in the treatment of BE are not clearly established. With regard to the antibiotic regimen, the combination of doxycycline and streptomycin has produced the best results in the treatment of different forms of brucellosis. In cases of BE, addition of rifampicine has been advocated because of its excellent tissue distribution, high penetration in valvular vegetations, and the possible toxicity of streptomycin after 3 weeks.<sup>17-19</sup> The results in our series can be considered very good, bearing in mind the embolic complications and the advanced state of tissue destruction in some patients.

Our patients received antibiotic treatment for at least 4–6 weeks preoperatively. Most (80,6%) of the patients received rifampicine (900 mg bid), doxycycline (200 mg/kg bid), and cotrimoxazole (15 mg/kg bid). Following surgical procedures patients continued their preoperative drug regimen.

In general, all over the world indications for surgery are mainly accepted as: valvular insufficiency resulting in refractory heart failure, sepsis caused by myocardial abscess and severe valvular involvement, and embolization. Acute onset of aortic insufficiency is a poor prognostic factor and heart failure due to aortic regurgitation mostly progresses rapidly. Worsening of valvular regurgitation and ventricular dysfunction may lead to gradual onset of CHF despite adequate antibiotic therapy.<sup>20</sup>

There have been no prospective outcome studies comparing early surgery with the conventional treatment strategy based on current guidelines. In our experience, the patients with brucella endocarditis should wait for operation at least four weeks, unless the complications of the brucellosis occur.

The preoperative condition of the patient, antibiotic therapy, surgical timing, perioperative management, surgical techniques, postoperative management, follow-up are important determinants for the results of surgery. Postoperative antibiotic treatment, radical debridement, and the method of reconstruction utilized are important factors for persistent and recurrent infection.<sup>21</sup>

In our retrospective study, combination of adequate medical and surgical therapy resulted in declined morbidity and mortality rate. The valve replacement with aggressive debridement is the most important part of the treatment, which must be supported with efficient preoperative and long term postoperative medical treatment. All practitioners as well as specialists must have a high degree of suspicion of brucellosis in endemic regions and all physicians must keep in mind that early diagnosis will change the course of the disease.

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