Published in final edited form as:

Ann Thorac Surg. 2012 December ; 94(6): 2141–2146. doi:10.1016/j.athoracsur.2012.07.006.

MEDICAL vs. MEDICAL AND SURGICAL TREATMENT FOR BRUCELLA ENDOCARDITIS: A REVIEW OF THE LITERATURE

Maryam Keshtkar-Jahromi, MD, MPH^{1,2}, Seyed-Mostafa Razavi, MD², Sharareh Gholamin, MD², Marzieh Keshtkar-Jahromi, MD², Mian Hossain, PhD^{3,4}, and Mohammad Sajadi, MD^{3,*}

¹Union Memorial Hospital, University of Maryland, Baltimore, USA

²Clinical Research and Development Center, Shahid Modarres Hospital, Shahid Beheshti University (MC), Tehran, Iran

³Institute of Human Virology, University of Maryland, Baltimore, MD, USA

⁴School of Community Health and Policy, Morgan State University, MD, USA

Abstract

This review was undertaken to determine the role of surgery in the treatment of brucella endocarditis. All English and French articles reporting brucella endocarditis (1966–2011) in Pubmed, Google and Scopus were reviewed. 308 cases were identified and Linear and Logistic regression was performed. Surgery improved outcomes by decreasing mortality from 32.7% in the medical treatment only group to 6.7% in the combined surgical and medical treatment group ($p < .001$). This association was still significant while controlling for other contributing factors. In the absence of a controlled trial, we recommend the utmost vigilance and consideration of surgical management in treating such patients.

Introduction

Brucella spp. are intracellular pathogens that are transmitted primarily through consumption of unpasteurized products, causing diverse clinical manifestations. The Mediterranean basin, Middle East, India, Mexico, and Central and South America are endemic regions. Brucellosis usually presents as fever without a focus. However, complications develop in 25–35% of patients, most commonly involving the osteoarticular system, followed by the genitourinary, central nervous and cardiovascular systems [1]. Endocarditis as a complication of brucellosis is only seen in 1–2% of patients in several published series [2, 3]. However, endocarditis accounts for 80% of these deaths due to brucellosis [4].

Brucella endocarditis has been reported in those with normal, damaged, or prosthetic valves. Before the introduction of open heart surgery, most cases of brucella endocarditis were treated medically and mortality was more than 80% [4]. Initially there was no clear evidence that antibiotics had any effect on the course of the disease as short courses of aureomycin, streptomycin, penicillin, and chloramphenicol all failed to be beneficial [5]. In 1955, the first successful treatment of *Brucella abortus* endocarditis using a long course of aureomycin and

© 2012 The Society of Thoracic Surgeons. Published by Elsevier Inc. All rights reserved.

*Address correspondence to Dr. Sajadi, Institute of Human Virology, University of Maryland School of Medicine, 725 W. Lombard St. (N548), Baltimore, MD 21201 (msajadi@ihv.umaryland.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

streptomycin was reported [6] and in 1966, for the first time, a case of severe *Brucella suis* endocarditis was treated surgically [7]. Since then, there have been reports of successful treatment with combined surgical and medical treatment [8–15]. However some cases of native or prosthetic valve brucella endocarditis have been cured by medical treatment alone [16–21].

Unfortunately, the treatment methods (medical, surgical, or both), the choice of antibiotics, and duration of medical treatment are not clear because of the low number of patients and lack of controlled trials. In this study, we reviewed all cases of brucella endocarditis reported cases since 1966 to evaluate the role of surgery in the treatment of brucella endocarditis.

Material and Methods

In a comprehensive search using “brucella endocarditis” and “brucella AND endocarditis” as keywords in Pubmed, Google and Scopus search engines, all articles in English and French reporting brucella endocarditis (January 1 1966 to July 22, 2011) were identified. We selected English and French as they are the most common languages used in medical literature. Reports prior to 1966 were excluded to eliminate potential bias related to limited antibiotic access and heart surgery techniques at that time. Letters to the editor, and cases of endocarditis with more than one organism were excluded. Additional cases were excluded because of very limited data. This left us with 121 articles, with 308 analyzable cases. 77 of these articles are included in the references section [1–3, 7–80], and the full list of these articles can be obtained from the corresponding author.

Age, gender, valve involvement (aortic, mitral, or both), country of origin, underlying heart disease, risk factors, blood or tissue culture and species isolated, serology titer, echocardiographic findings, vegetation size (surface area) intra and extra cardiac complications, heart failure, treatment method (medical alone versus medical plus surgical), antibiotic regimen, duration of medical treatment, and outcome (dead or alive) were recorded to assess the effect on survival. Death was defined as life loss within a year of diagnosis which was related to brucella, endocarditis or its complications. Such a long time for death definition was chosen because of the length of therapy of brucella endocarditis, which could be up to a year. All data that was extracted was independently verified by a second member of the team.

Linear and Logistic regression was performed to assess the role of surgery in treatment of brucella endocarditis in this study. Data from 308 cases were analyzed based on their treatment (medical vs. combined medical and surgical) regimen and outcome. Other variables affecting outcome were also considered. The predictor variables which were not highly correlated among themselves were kept in the initial multivariate logistic regression model. The variables which are found independently significant were finally kept in the multivariate logistic regression model. Logistic and linear regression was done with STATA statistical software (College Station, TX). Statistical analysis was performed with Graph Pad Prism (San Francisco, CA) for the Mann-Whitney and Fisher's exact tests. P values <0.05 were considered statistically significant.

Results

308 cases of brucella endocarditis patients (1966–2011) were reviewed and analyzed to assess the role of surgery in treatment (Table 1). Turkey (41.9%) and Iran (10.1%) had the most reported cases, and 95% of cases were from countries in the Middle East or Mediterranean regions. The majority (60.3%) were diagnosed with brucellosis prior to

endocarditis. Diagnosis was made by serology or culture in all but one patient (who was PCR positive only), with 82.5% of patients being infected with *Brucella melitensis* and 14.0% with *Brucella abortus*.

Endocarditis developed primarily on those with diseased valves or underlying structural heart defects, although 32.6% did not have any underlying heart or valvular defects. The aortic valve was the most commonly involved valve, and the average size of the vegetations was large (mean vegetation surface area of 118.3 mm²) (Table 2). Intracardiac abscess was seen in 20.5% of patients and the majority of patients had congestive heart failure (59.1%).

Combination medical and surgical treatment was undertaken in 77.6%, with 22.4% receiving medical care only. Patients did not receive surgery for a variety of reasons which included the following: the patient was considered to be a high risk candidate for surgery, there was no definite indication for surgery, surgery was unavailable, or refusal of patients to consent to surgery. The most commonly used antimicrobial regimen consisted of rifampin, tetracycline, and an aminoglycoside or cotrimoxazole (Table 3). However, the choice of antibiotics, antibiotic regimens or the length of treatment with antibiotics did not show any significant affect on patient outcome.

Mortality was 32.7% (17 of 69) in the medical treatment only group compared to 6.7% (16 of 239) in the combined medical and surgical treatment group ($p<.001$). Mortality was increased with medical treatment alone (OR 15.44, 95% CI 4.32–55.14), or presence of congestive heart failure (OR 2.05, 95% CI 1.06–14.18). A positive blood culture was associated with decreased mortality (OR .21, 95% CI .06–.68). Most isolates were *Brucella melitensis* but the type of isolate (*melitensis* vs. *abortus*) did not affect mortality ($p=1.0$). The presence of prosthetic valve endocarditis did not significantly increase mortality compared to native valves. Please refer to Table 4 for a summary of the above.

Comment

In the past, human brucellosis was a prevalent disease in the United States, but immunization of cattle and federal eradication programs have controlled this zoonosis [25]. *Brucella* endocarditis was first reported in 1906 and a total of 56 cases were recorded until 1960 [1]. Most cases reported prior to the antibiotic and cardiac surgery era were derived from postmortem data [4]. By necropsy, endocarditis was found in 35 out of 44 patients who had died of brucellosis (80%) [4].

Brucella endocarditis is typically a slowly destructive process, with a high tendency to tissue ulceration, leading to large vegetations that are difficult to treat with medical treatment alone [4]. The endocardial lesions of brucellosis are the result of direct invasion of endocardium by the organisms. A review of valvular lesion in 20 patients who died because of *Brucella* endocarditis showed micro-abscesses within the valve cusps, destruction of the commissures, and the nodular calcific deformation, indicating that this is a chronic bacterial endocarditis [4]. There was no evidence of hypersensitivity reaction or arteritis.

This propensity of *brucella* to cause endocarditis associated with cardiac abscesses (20.5% in this review), large vegetations (mean 118.3 mm² in this review), and devastating complications (see Table 2), as well as the need for a minimum of several antibiotics for minimum control of the infection has made surgery a mainstay of treatment compared to endocarditis caused by other organisms.

Currently, surgery for *brucella* endocarditis has been usually considered if bulky vegetation, abscess, aneurysm, paravalvular leak, or valvular malfunction is present [28]. Surgery is also recommended for prosthetic valve *brucella* endocarditis or *brucella* infection of cardiac

devices (e.g., implantable cardioverter-defibrillator). On the other hand, some patients with brucella endocarditis have been cured by medical treatment alone [16–21].

Although most authorities believe that surgery plays a significant role in treatment of brucella endocarditis, this study is the first to demonstrate that surgery is significantly associated with improved survival. Those who did not receive surgery had a significantly elevated risk of mortality (Hazard Ratio OR 15.44, 95% CI 4.32–55.14).

Positive blood culture was also a protective factor against death. A negative culture could potentially lead to a delay in diagnosis and treatment, explaining how it could be a risk factor for death. In this review, the majority of patients were first diagnosed with brucellosis before endocarditis was suspected, thus a positive culture may have aided in earlier diagnosis and treatment. Unexpectedly, Brucella endocarditis on a prosthetic valve was not significantly associated with higher mortality compared to native valves which might be related to possible undocumented co-variables or low number of cases in our study. However, given that most patients (80%, or 40 of 50) with prosthetic valve endocarditis underwent surgery and only one of these died (compared to 2 deaths out of 10 in the medical therapy only group), it may be that the improved benefit on mortality with surgery is seen whether or not patients have prosthetic valve endocarditis.

Heart failure as a presenting symptom is expected to increase mortality, mostly as a consequence of valvular dysfunction. In this study, those who presented with congestive heart failure signs and symptoms had higher mortality (Hazard Ratio 2.05, 95% CI 1.06–14.18).

There is no reliable data regarding the choice of antibiotic regimen, and different treatment durations have been recommended by different authorities. Control of infection with preoperative antibiotic therapy and immediate surgery after clinical stabilization has also been recommended [30]. The intracellular location of the microorganism makes it inaccessible to the action of many antibiotics [31]. Ideally, the antimicrobial agent should be bactericidal to prevent relapse in brucellosis [32]. In a case series study from Turkey (10 cases), the addition of a third generation cephalosporin, ceftriaxone, to the combination of a tetracycline group and rifampicin was more effective than aminoglycosides [22]. In the current review, different antibiotic regimens or use of specific antibiotics were not significantly associated with mortality. There seems to be unanimous agreement that therapy should be prolonged (some have treated for greater than one year); although no clear duration has yet been established. Based on the current study, we can not make any recommendations regarding the choice of antibiotic regimen or the duration of treatment.

Although this review is the largest one evaluating the role of surgery up to this time, it relies entirely on retrospectively published data. The lack of published trials (due to low number of cases reported annually worldwide) meant a reliance on case series and case reports that have the potential for selection bias. In addition, because the review spanned many decades, and because the diagnosis, definition, and treatment of endocarditis have undergone changes during this time, this must be considered a limitation in interpreting the data. However, despite these shortcomings, there appears to be a large benefit in those who received surgical intervention.

In conclusion, in this review we demonstrate that brucella endocarditis presents with many associated conditions in which surgery should be considered. For example, the mean vegetation size was rather large at 118.3 mm², 59.1% had reported CHF, and 20.5% had intracardiac abscess. According to the AHA 2005 guidelines, the only microorganisms in which surgery is considered regardless of other findings are “fungal IE” and “left-sided endocarditis with Gram-negative bacteria such as *S marcescens* and *Pseudomonas* species.”

Given the severity of the initial illness, the multiple antibiotics needed to control this infection, and the improved outcome with surgery, we believe that *Brucella* species may need to be considered as an indication for surgery in addition to the microorganisms listed above. In clinical practice, this is often the case (77.6% of the patients in the literature have undergone surgery). We believe this review provides some data to back up this practice, and for further research to be done until the issue is fully resolved. Although there are still some other controversial issues in management of brucella endocarditis in terms of choice of antibiotic treatment and duration of treatment, based on the result of this review and absence of a well-designed clinical trial, we recommend the utmost vigilance and consideration of surgical management in treating such patients.

References

1. Valliattu J, Shuhaiber H, Kiwan Y, Araj G, Chugh T. Brucella endocarditis. Report of one case and review of the literature. *J Cardiovasc Surg.* 1989; 30(5):782–5. [PubMed: 2681218]
2. Ferreira P, Gama P, Correia J, et al. Brucella endocarditis--case report and literature review. *Rev Port Cardiol.* 2008; 27(10):1309–15. [PubMed: 19178031]
3. Memish Z, Mah MW, Al Mahmoud S, Al Shaalan M, Khan MY. Brucella bacteraemia: clinical and laboratory observations in 160 patients. *J Infect.* 2000; 40(1):59–63. [PubMed: 10762113]
4. Peery TM, Belter LF. Brucellosis and heart disease. II. Fatal brucellosis: a review of the literature and report of new cases. *Am J Pathol.* 1960; 36:673–97. [PubMed: 14431371]
5. Hart FD, Morgan A, Lacey B. Brucella abortus endocarditis. *Br Med J.* 1951; 1 (4714):1048–53. [PubMed: 14830836]
6. Hudson RA. Brucella abortus endocarditis; a case. *Circulation.* 1957; 16(3):411–3. [PubMed: 13461249]
7. Golden B, Layman TE, Koontz FP, Mergner WJ. Brucella suis endocarditis. *South Med J.* 1970; 63(4):392–5. [PubMed: 5467309]
8. Duran E, Sunar H, Ege T, Canbaz S, Akata F, Özbay G. Excision of Aortic Vegetation in Brucella Endocarditis. *Asian Cardiovasc and Thorac Annals.* 2001; 9(1):59–61.
9. Hadjinikolaou L, Triposkiadis F, Zairis M, Chlapoutakis E, Spyrou P. Successful management of Brucella mellitensis endocarditis with combined medical and surgical approach. *Eur J Cardiothorac Surg Jun.* 2001; 19(6):806–10.
10. Heibig J, Beall AC Jr, Myers R, Harder E, Feteih N. Brucella aortic endocarditis corrected by prosthetic valve replacement. *Am Heart J.* 1983; 106(3):594–6. [PubMed: 6881037]
11. Inan MB, Eyileten ZB, Ozcinar E, et al. Native valve Brucella endocarditis. *Clin Cardiol.* 2010; 33(2):E20–6. [PubMed: 20043343]
12. Jacobs F, Abramowicz D, Vereerstraeten P, Le Clerc JL, Zech F, Thys JP. Brucella endocarditis: the role of combined medical and surgical treatment. *Rev Infect Dis.* 1990; 12(5):740–4. [PubMed: 2237111]
13. Juffé A, Montes J, Montero CG, et al. Emergency aortic valve replacement in Brucella endocarditis: report of two cases. *Tex Heart Inst J.* 1983; 10(3):315–7. [PubMed: 15227119]
14. Keshtkar-Jahromi M, Boroumand MA, Razavi SM, et al. Brucella Endocarditis, A Report Of 14 Cases (1991–2009). *J Infect.* 2010; 61(1):89–92. [PubMed: 20362000]
15. Kalaycioglu S, Imren Y, Erer D, Zor H, Arman D. Brucella Endocarditis with Repeated Mitral Valve Replacement. *J Card Surg.* 2005; 20(2):189–92. [PubMed: 15725149]
16. Karaoglan I, Namiduru M, Baydar I, et al. Three Cases of Brucella Prosthetic Valve Endocarditis Cured With Medical Treatment. *Ankem Dergisi.* 2009; 23 (1):46–49.
17. Cisneros JM, Pachón J, Cuello JA, Martinez A. Brucella endocarditis cured by medical treatment. *J Infect Dis.* 1989; 160(5):907. [PubMed: 2809266]
18. Mohandas N, Balasubramanian R, Prasad SB. Can brucella endocarditis be treated successfully with medical therapy alone? *Trop Doct.* 2009; 39(2):123–4. [PubMed: 19299306]
19. Cohen N, Golik A, Alon I, et al. Conservative treatment for Brucella endocarditis. *Clin Cardiol.* 1997; 20(3):291–4. [PubMed: 9068918]

20. Mert A, Kocak F, Ozaras R, et al. The role of antibiotic treatment alone for the management of Brucella endocarditis in adults: a case report and literature review. *Ann Thorac Cardiovasc Surg.* 2002; 8(6):381–5. [PubMed: 12517300]
21. Murdaca G, Colombo BM, Caiti M, Cagnati P, Massa G, Puppo F. Remission of brucella endocarditis in a patient with mitral valve mechanical prosthesis by antibiotic therapy alone: a case report. *Int J Cardiol.* 2007; 117(1):e35–6. [PubMed: 17275109]
22. Cay S, Cagirci G, Maden O, Balbay Y, Aydogdu S. Brucella endocarditis - a registry study. *Kardiolog Pol.* 2009; 67(3):274–80. [PubMed: 19378233]
23. Caylan R, Keske S, Durmaz T, Keles T, Tasyaran MA. A case of Brucella endocarditis in association with superficial femoral artery thrombus. *Trop Doct.* 2009; 39(4):251–2. [PubMed: 19762588]
24. Park SH, Choi YS, Choi YJ, Cho SH, Yoon HJ. Brucella endocarditis with splenic abscess: a report of the first case diagnosed in Korea. *Yonsei Med J.* 2009; 50(1):142–6. [PubMed: 19259361]
25. Fernández-Guerrero ML. Zoonotic endocarditis. *Infect Dis Clin North Am.* 1993; 7(1):135–52. [PubMed: 8463649]
26. Flugelman MY, Galun E, Ben-Chetrit E, Caraco J, Rubinow A. Brucellosis in patients with heart disease: when should endocarditis be diagnosed? *Cardiology.* 1990; 77(4):313–7. [PubMed: 2073648]
27. Kele C, Bozbu a N, Si mano lu M, et al. Surgical treatment of Brucella endocarditis. *Ann Thorac Surg.* 2001; 71(4):1160–3. [PubMed: 11308153]
28. Sasmazel A, Baysal A, Fedakar A, et al. Treatment of Brucella endocarditis: 15 years of clinical and surgical experience. *Ann Thorac Surg.* 2010; 89(5):1432–6. [PubMed: 20417757]
29. Esmailpour N, Borna S, Nejad MR, Badie SM, Badie BM, Hadadi A. Brucella endocarditis: a report from Iran. *Trop Doct.* 2010; 40(1):47–9. [PubMed: 19850601]
30. Ozsöyler I, Yilik L, Bozok S, et al. Brucella endocarditis: the importance of surgical timing after medical treatment (five cases). *Prog Cardiovasc Dis.* 2005; 47(4):226–9. [PubMed: 15991151]
31. Al-Harthi SS. The morbidity and mortality pattern of Brucella endocarditis. *Int J Cardiol.* 1989; 25(3):321–4. [PubMed: 2613379]
32. al Kasab S, al Fagih M, al Rasheed A, et al. Management of Brucella endocarditis with aortic root abscess. *Chest.* 1990; 98(6):1532–4. [PubMed: 2245705]
33. Tasdemir K, Kaya MG, Mavili E, et al. Surgical approach to the management of Brucella endocarditis. *Eur J Cardiothorac Surg.* 2010; 37(5):1021–4. [PubMed: 20036135]
34. Gunes Y, Tuncer M, Guntekin U, et al. Clinical characteristics and outcome of Brucella endocarditis. *Trop Doct.* 2009; 39(2):85–8. [PubMed: 19299289]
35. Botta L, Bechan R, Yilmaz A, Di Bartolomeo R. Prosthetic valve endocarditis due to Brucella: successful outcome with a combined strategy. *J Cardiovasc Med.* 2009; 10(3):257–8.
36. Yildiz A, Tufekcioglu O, Aras D, Ozeke O, Celenk MK, Sasmazel A. Myocardial noncompaction presenting with Brucella endocarditis. *Int J Cardiol.* 2009; 131(3):e87–9. [PubMed: 17931725]
37. Tuncer M, Ekim H, Güne Y, Güntekin U. Atrial septal defect presenting with Brucella endocarditis. *Circ J.* 2008; 72(12):2096–7. [PubMed: 18854616]
38. Je HG, Song H. Brucella endocarditis in a non-endemic country: first reported case in East Asia. *Circ J.* 2008; 72(3):500–1. [PubMed: 18296855]
39. Katirciba i MT, Koçum HT, Cölkesen AY, Tekin A, Sezgin AT. Management of Brucella endocarditis on native mitral valve in a patient with prosthetic aortic valve: a case report. *Int J Cardiol.* 2008; 129(2):300–1. [PubMed: 17659796]
40. Koumallos N, Paschalis A, Antoniadis C, et al. Valve replacement for Brucella endocarditis: two case reports. *Int J Cardiol.* 2008; 127(2):e83–5. [PubMed: 17651833]
41. Biyik I, Oto O, Ergene O. Brucella pancarditis with dissecting aortic root abscess, left ventricular pseudoaneurysm and ventricular septal defect. *J Int Med Res.* 2007; 35(3):422–6. [PubMed: 17593872]

42. Dourakis S, Sambatakou H, Tsiachris D, Kittou N, Alexopoulou A, Archimandritis A. A 70-year-old stock-breeder with tricuspid valve and defibrillator lead brucella endocarditis. *Int J Cardiol.* 2008; 126(3):e47–9. [PubMed: 17395320]
43. Purwar S, Metgud SC, Darshan A, Mutnal MB, Nagmoti MB. Infective endocarditis due to brucella. *Indian J Med Microbiol.* 2006; 24(4):286–8. [PubMed: 17185849]
44. Sayar N, Terzi S, Yilmaz HY, et al. A case of prosthetic mitral valve Brucella endocarditis complicated with torsades de pointes. *Heart Vessels.* 2006; 21(5):331–3. [PubMed: 17151824]
45. Al Dahouk S, Schneider T, Jansen A, et al. Brucella endocarditis in prosthetic valves. *Can J Cardiol.* 2006; 22(11):971–4. [PubMed: 16971982]
46. Tasbakan MI, Yamazhan T, Arda B, et al. Tissue culture positive prosthetic aortic valve Brucella endocarditis. *Ir J Med Sci.* 2006; 175(2):84. [PubMed: 16872039]
47. Ozkokeli M, Sensoz Y, Kayacioglu I, et al. Treatment of Brucella endocarditis: our surgical experience with 6 patients. *Heart Surg Forum.* 2005; 8(4):E262–5. [PubMed: 16024329]
48. Alhyari AR, Bakri FG, Al-Mousa EN, Al-Smady MM. Successful treatment of Brucella endocarditis with aortic root abscess. *Saudi Med J.* 2005; 26(3):473–5. [PubMed: 15806223]
49. Yavuz T, Ozaydin M, Ulasan V, Ocal A, Ibrisim E, Kutsal A. A case of mitral stenosis complicated with seronegative Brucella endocarditis. *Jpn Heart J.* 2004; 45(2):353–8. [PubMed: 15090714]
50. Erbay AR, Turhan H, Dogan M, Erbasi S, Cagli K, Sabah I. Brucella endocarditis complicated with a mycotic aneurysm of the superior mesenteric artery: a case report. *Int J Cardiol.* 2004; 93(2–3):317–9. [PubMed: 14975571]
51. Yilmaz MB, Kisacik HL, Korkmaz S. Persisting fever in a patient with brucella endocarditis: occult splenic abscess. *Heart.* 2003; 89(7):e20. [PubMed: 12807868]
52. Reguera JM, Alarcón A, Miralles F, Pachón J, Juárez C, Colmenero JD. Brucella endocarditis: clinical, diagnostic, and therapeutic approach. *Eur J Clin Microbiol Infect Dis.* 2003; 22(11):647–50. [PubMed: 14566576]
53. Sharivker D, Vazan A, Varkel J. Brucella endocarditis complicated by acute glomerulonephritis--early surgical intervention. *Acta Cardiol.* 2001; 56(6):399–400. [PubMed: 11791809]
54. Rahman A, Burma O, Felek S, Yekeler H. Atrial septal defect presenting with Brucella endocarditis. *Scand J Infect Dis.* 2001; 33(10):776–7. [PubMed: 11728049]
55. Alsoub H. Brucella infective endocarditis: a report of four successfully treated patients. *Clin Microbiol Infect.* 2001; 7(7):382–5. [PubMed: 11531987]
56. Kula S, Erer D, Büyükkates M, Tunaoglu FS, Olguntürk R, Ozdogan EM. Brucella endocarditis: case report and review of the literature. *J Heart Valve Dis.* 2001; 10(4):486–8. [PubMed: 11499595]
57. Akinci E, Gol MK, Balbay Y. A case of prosthetic mitral valve endocarditis caused by Brucella abortus. *Scand J Infect Dis.* 2001; 33(1):71–2. [PubMed: 11234984]
58. Ying W, Nguyen MQ, Jahre JA. Brucella canis endocarditis: case report. *Clin Infect Dis.* 1999; 29(6):1593–4. [PubMed: 10585833]
59. Cakalagaoglu C, Keser N, Alhan C. Brucella-mediated prosthetic valve endocarditis with brachial artery mycotic aneurysm. *J Heart Valve Dis.* 1999; 8(5):586–90. [PubMed: 10517403]
60. Arslan H, Korkmaz ME, Kart H, Gül C. Management of brucella endocarditis of a prosthetic valve. *J Infect.* 1998; 37(1):70–1. [PubMed: 9733385]
61. Uddin MJ, Sanyal SC, Mustafa AS, et al. The role of aggressive medical therapy along with early surgical intervention in the cure of Brucella endocarditis. *Ann Thorac Cardiovasc Surg.* 1998; 4(4):209–13. [PubMed: 9738123]
62. Leandro J, Roberto H, Antunes M. Brucella endocarditis of the aortic valve. *Eur J Cardiothorac Surg.* 1998; 13(1):95–7. [PubMed: 9504738]
63. Elzouki AY, Akthar M, Mirza K. Brucella endocarditis associated with glomerulonephritis and renal vasculitis. *Pediatr Nephrol.* 1996; 10(6):748–51. [PubMed: 8971897]
64. Quiroga J, Miralles A, Farinola T, et al. Surgical treatment of Brucella endocarditis. *Cardiovasc Surg.* 1996; 4(2):227–30. [PubMed: 8861443]

65. Saadeh AM, Abu-Farsakh NA, Omari HZ. Infective endocarditis and occult splenic abscess caused by *Brucella melitensis* infection: a case report and review of the literature. *Acta Cardiol*. 1996; 51(3):279–85. [PubMed: 8817011]
66. Schvarcz R, Svedenhag J, Rådegran K. A case of *Brucella melitensis* endocarditis successfully treated by a combination of surgical resection and antibiotics. *Scand J Infect Dis*. 1995; 27(6):641–2. [PubMed: 8685649]
67. Sungur C, Sungur A, Gedikoglu G, et al. Fatal *Brucella melitensis* endocarditis in a hemodialysis patient. *Nephron*. 1994; 67(2):234–5. [PubMed: 8072615]
68. Kumar N, Prabhakar G, Kandeel M, et al. *Brucella* mycotic aneurysm of ascending aorta complicating discrete subaortic stenosis. *Am Heart J*. 1993; 125(6):1780–2. [PubMed: 8498327]
69. Chan R, Hardiman RP. Endocarditis caused by *Brucella melitensis*. *Med J Aust*. 1993; 158(9):631–2. [PubMed: 8479384]
70. Delvecchio G, Fracassetti O, Lorenzi N. *Brucella* endocarditis. *Int J Cardiol*. 1991; 33(2):328–9. [PubMed: 1743797]
71. Micozzi A, Venditti M, Gentile G, Alessandri N, Santero M, Martino P. Successful treatment of *Brucella melitensis* endocarditis with pefloxacin. *Eur J Clin Microbiol Infect Dis*. 1990; 9(6):440–2. [PubMed: 2387299]
72. Al-Mudallal DS, Mousa AR, Marafie AA. Apyrexia *Brucella melitensis* aortic valve endocarditis. *Trop Geogr Med*. 1989; 41(4):372–6. [PubMed: 2635455]
73. Skillington PD, McGiffin DC, Kemp R, Bett JH, Holt G, Forgan-Smith R. Brucellosis complicated by aortic valve endocarditis. *Aust N Z J Med*. 1988; 18(7):872–3. [PubMed: 3250411]
74. al-Kasab S, al-Fagih MR, al-Yousef S, et al. *Brucella* infective endocarditis. Successful combined medical and surgical therapy. *J Thorac Cardiovasc Surg*. 1988; 95(5):862–7. [PubMed: 3258947]
75. Jeroudi MO, Halim MA, Harder EJ, Al-Siba'I MB, Ziady G, Mercer EN. *Brucella* endocarditis. *Br Heart J*. 1987; 58(3):279–83. [PubMed: 3311098]
76. Fernández-Guerrero ML, Martinell J, Aguado JM, Ponte MC, Fraile J, de Rábago G. Prosthetic valve endocarditis caused by *Brucella melitensis*. A report of four cases successfully treated with tetracycline, streptomycin, and sulfamethoxazole and trimethoprim plus valve replacement. *Arch Intern Med*. 1987; 147(6):1141–3. [PubMed: 3592879]
77. Abu Romeh SH, Kozma GN, Johnny KV, Sabha M. *Brucella* endocarditis causing acute renal failure. *Nephron*. 1987; 46(4):388–9. [PubMed: 3658070]
78. Lubani M, Sharda D, Helin I. Cardiac manifestations in brucellosis. *Arch Dis Child*. 1986; 61(6):569–72. [PubMed: 3729526]
79. Almér LO. A case of brucellosis complicated by endocarditis and disseminated intravascular coagulation. *Acta Med Scand*. 1985; 217(1):139–40. [PubMed: 3976429]
80. Syrjamäki C, Migliazzo A, Yarbrough JW, Meyer LE. *Brucella abortus* endocarditis following ingestion of cow's blood. *Nebr Med J*. 1984; 69(5):141–2.

Table 1

Demographic variables and risk factors for brucella endocarditis patients (1966–2011)

Indicators/variables	Percentages	Mean (Range)
Mean age, years (n=294)	-	41.0 (5–77)
Sex (n=295)		
Male	75.3	-
Female	24.7	-
Country (n=308)		
Turkey	41.9	-
Iran	10.1	-
Spain	8.8	-
Saudi Arabia	8.1	-
Italy	6.5	-
Greece	3.9	-
France	3.6	-
Other	17.2	-
Predisposing cardiac condition (n=233)		
No underlying condition	32.6	-
Prosthetic valve	21.0	-
Rheumatic heart disease	15.5	-
Bicuspid aortic valve	7.3	-
Aortic stenosis	6.4	-
Aortic regurgitation	5.6	-
Mitral Stenosis	3.4	-
Other cardiac defects	7.3	-
Risk Factor (n=151)		
Unpasteurized dairy consumption only	51.0	-
Animal contact only	29.8	-
Unpasteurized dairy and animal contact	13.2	-
None reported	6.0	-

Table 2

Clinical presentations, complications, diagnostic and echocardiographic findings of brucella endocarditis (1966–2011)

Indicators	Percentages	Mean (Range)
Presentation		
Mean duration of symptoms (n=170)	-	99.7 days (2–450)
Presence of CHF (n=225)	59.1	-
Brucellosis initially suspected (n=209)	60.3	-
Endocarditis initially suspected (n=209)	39.7	-
Diagnosis		
Blood culture positive (n=228)	68.4	-
Mean Wright's titer (n=217)	-	1:2089 (0–30,000)
Mean 2ME titer (n=33)	-	1:4274 (40–30,000)
Mean Coomb's titer (n=18)	-	1:6773 (320–20,480)
Valve culture positive (n=99)	46.5	-
PCR (n=6)	100.0	-
Mean sedimentation rate (n=144)	-	54.2 (1–138)
Infecting strain (n=143)		
<i>Brucella melitensis</i>	82.5	-
<i>Brucella abortus</i>	14.0	-
<i>Brucella canis</i>	2.1	-
<i>Brucella suis</i>	1.4	-
Valvular Involvement (n=248)		
Aortic only	61.7	-
Mitral only	23.4	-
Aortic and mitral	10.9	-
Other	4.0	-
Cardiac Findings		
Intracardiac abscess (n=234)	20.5	-
Mean vegetation size, mm (n=68)	-	118.3 (6–625)
Complications (n=308)		
CVA	6.2	-
Embolic event (excluding brain)	3.6	-
Arrhythmia	3.6	-
Renal failure	3.6	-
Glomerulonephritis	3.2	-
Splenic abscess	1.0	-

Table 3

Treatment of brucella endocarditis (1966–2011)

Indicators	Percentages
Therapy (n=308)	
Combined surgical and medical therapy	77.6
Medical therapy only	22.4
Antibiotic Regimens (n=288)	
Rifampin + Tetracycline + Cotrimoxazole	26.7
Rifampin + Tetracycline + Aminoglycoside	24.3
Tetracycline + Aminoglycoside	9.4
Rifampin + Tetracycline + Ceftriaxone	8.3
Rifampin + Tetracycline	8.0
Tetracycline + Aminoglycoside + Cotrimoxazole	6.3
Other	17.0
Surgical treatment (n=197)	
Aortic valve replacement	67.5
Mitral valve replacement	17.3
Aortic and mitral valve replacement	13.7
Other	1.5

Table 4

Risk factors for death in patients with brucella endocarditis

Risk factor	Hazard Ratio	Association ^a	95% CI ^b
Medical treatment only	15.44	<0.001	4.32 – 55.14
Positive blood culture	0.21	0.01	0.06 – 0.68
Congestive heart failure	2.05	0.04	1.06 – 14.18
Mitral valve involvement	0.28	0.062	0.08 – 1.06
Year of diagnosis	1.04	0.229	0.98 – 1.11
Age > 50	0.44	0.268	0.11 – 1.87
Age 30–49	0.69	0.574	0.19 – 2.53
Female sex	0.79	0.738	0.20 – 3.12
Prosthetic valve endocarditis	1.02	0.979	0.23 – 4.43

^a Association is expressed as the *p* value derived from a chi-square test.

^b Confidence interval.