

Brucella endocarditis

M OUSSAMA JEROUDI,* MURTADA A HALIM,† EDWARD J HARDER,
M BADAWI AL-SIBA'I, GALAL ZIADY, EDWARD N MERCER

From the Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

SUMMARY *Brucella* endocarditis is an underdiagnosed, fatal complication of human brucellosis. Four successfully treated cases of *Brucella* endocarditis are reported. The development of a new valvar lesion and bulky vegetations seen on echocardiography helped to identify *Brucella* endocarditis occurring during systemic brucellosis. The aortic valve was affected in all four patients, and in one the mitral valve was also affected. Medical treatment did not cure the patients and all needed valve replacement—for haemodynamic deterioration in three and because a further embolism was feared in one. Antibiotics were continued for six to nine months after operation. There was no early or late mortality and no recurrence after a follow up of 15 months.

Brucellosis is a very common disease; according to the World Health Organisation 500 000 new cases, mainly caused by *Brucella melitensis*, are reported annually.¹ The disease is underdiagnosed and underreported; some authorities estimate that for each case reported another 26 are not recognised or not reported.^{2 3}

Human brucellosis is usually caused by one of three species of the genus *Brucella*: *melitensis*, *abortus*, and *suis*; it is rarely caused by *Brucella canis*.³ Brucellae are small, non-motile, gram negative capnophilic coccobacilli with optimum growth at temperature of 37°C and a pH of 6.6-6.8. Brucellosis is found primarily in animals and is spread to man by direct contact with infected tissue or by ingestion of infected animal products, most commonly milk or milk products. In Western countries, brucellosis is an occupational disease found mainly in farmers, people working in meat packing plants, veterinary surgeons, and livestock producers. In other areas of the world the disease is more widespread and is found in the general population.

*Present address: Methodist Hospital, Division of Cardiology, 6535 Fannin MSF 905, Houston, Texas 77030, USA.

†Present address: Riyadh Armed Forces Hospital, PO Box 7897, Riyadh 11159, Saudi Arabia.

Requests for reprints to Dr M Badawi Al-Siba'i, Department of Medicine, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia.

Accepted for publication 8 May 1987

Cardiovascular complications of systemic brucellosis include endocarditis, myocarditis, and pericarditis, and these are the most common causes of death in brucellosis.⁴⁻⁶

There are only six reported cases of surgically cured *Brucella* endocarditis⁷⁻¹²; we report an additional four cases.

Patients and methods

Between January 1980 and January 1986 *Brucella* endocarditis was diagnosed in four patients referred to King Faisal Specialist Hospital. One of these patients has been the subject of an earlier report.¹² The diagnosis of endocarditis was established by the development of a new murmur and the presence of a vegetation on echocardiograms obtained during the course of systemic brucellosis, and was further supported by cardiac surgical findings and histopathology.

The following data were collected: symptoms at presentation, total and differential white blood cell count, erythrocyte sedimentation rate, electrocardiogram, serology, and blood culture. Serology included a Brucelloslide test (Bio Merienst) followed by a *Brucella* antibody tube dilution titre (Wellcome Diagnostics). Blood cultures were drawn and incubated in a supplemental yeast-peptone broth (Beckton-Dickinson). Initially kept in a vacuum, the cultures were exposed to air on day 7 and were thereafter incubated in an atmosphere of 5%-10% carbon dioxide. Subcultures on to blood agar plates were

Table Symptoms on admission

	Patients			
	1	2	3	4
Age and sex	25 M	62 M	42 M	32 M
Ingestion of raw milk	+	+	+	+
Duration of fever	6 mth	2 mth	11 mth	4 mth
Malaise or weight loss	+	+	+	+
Night sweats	+	+	+	+
Dyspnoea	+	+	+	+
Functional class NYHA	IV	II	II	II
Embolic episodes	—	Coronary	CVA	—
Known heart disease	—	—	—	—

NYHA, New York Heart Association; CVA, cardiovascular accident.

made weekly and kept for four days. Surgical specimens were cultured in thioglycolate broth, and inoculated on to routine culture media. All cultures identified as possibly containing fastidious organisms were kept for six weeks. Cultures containing pale-staining Gram negative coccobacillary rods that were both oxidase-positive and urease-positive were identified as brucellae. *Brucella* titres were measured and blood cultures performed on all patients on admission, at operation, and every three months for a year. M mode and cross sectional echocardiography was performed on all patients and Doppler echocardiography on all except patient 1. Patients 1 and 2 had right and left cardiac catheterisation.

Results

SYMPTOMS (Table)

All four patients were men aged 25–62 (mean 40). Symptoms had appeared two to eleven months before admission. At the time of admission, one patient was in New York Heart Association class IV and three were in class II; two of the latter deteriorated to class IV. Two patients (cases 2 and 3) had systemic embolisation to the coronary and cerebral arteries respectively. No patient had a known history of valvar heart disease.

PHYSICAL SIGNS

All patients were febrile and all had splenomegaly; one patient had finger clubbing. The aortic valve was affected in all patients; in one the mitral valve was also affected. Patient 1 was admitted with aortic regurgitation and acute pulmonary oedema. Two patients (cases 2 and 4) developed sudden severe, aortic regurgitation while in hospital receiving treatment and acute pulmonary oedema developed.

INVESTIGATIONS

Three patients had a normal white cell count (4900–7600/mm³) and one had leucopenia

(2900/mm³). The erythrocyte sedimentation rate was increased in three patients (range 56–85 mm/h) and was normal (6 mm/h) in one patient.

Electrocardiography showed sinus rhythm in all patients and none developed conduction disturbance. The patient with coronary embolism developed ventricular tachycardia and later ST-T wave changes.

Echocardiography showed a vegetation on the aortic valve in all patients; patient 4 had an additional vegetation on the mitral valve (fig 1). All vegetations were bulky, and in patient 3 the vegetation was pedunculated and prolapsing into the left ventricular outflow tract. Premature closure of the mitral valve indicative of acute aortic regurgitation was seen in patients 1, 2, and 4. Pulsed Doppler performed in the last three patients showed appreciable aortic regurgitation in all, with additional mitral regurgitation in one patient.

Serology showed a very high *Brucella* titre (range 2560–16 000) in all patients. Despite medical treatment all titres remained high or increased from the time of admission up to the time of operation (fig 2).

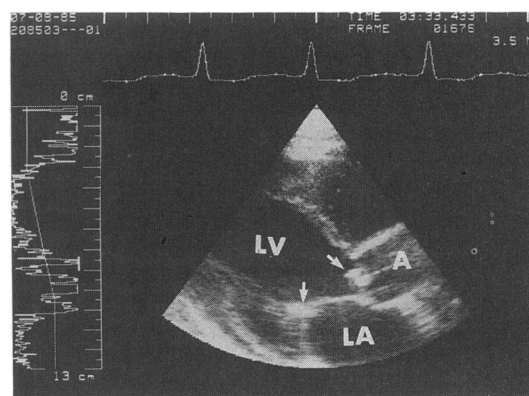


Fig 1 Parasternal long axis cross sectional echocardiogram of patient 4 showing vegetations of the aortic and mitral valves (arrows).

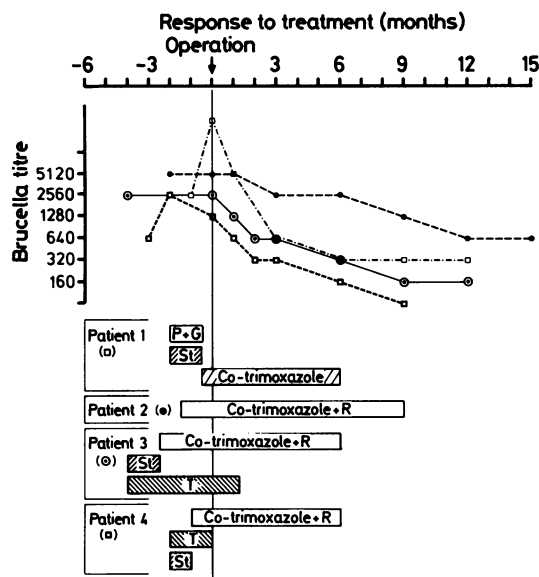


Fig 2 *Brucella* titres and response to treatment. Co-trimoxazole (trimethoprim + sulphamethoxazole); St, streptomycin; T, tetracycline; R, rifampicin; P + G, penicillin and gentamicin.

Six blood cultures were taken from each patient but only patient 3 had a blood culture that was positive for *Brucella melitensis* (the only biotype that was sought).

Cardiac catheterisation was performed in two patients (cases 1 and 4). In neither was an attempt made to cross the aortic valve for fear of embolism. Aortography showed severe aortic regurgitation in both and moderate mitral regurgitation in patient 4. The condition of patient 1 deteriorated further after angiography but he was stabilised and sent for operation the next day.

TREATMENT

Whatever the medical treatment the patients received before referral we elected to treat all patients in our institution with co-trimoxazole [Septra] (trimethoprim 10 mg/kg/day and sulphamethoxazole 20 mg/kg/day) and rifampicin 300–600 mg/day, except patient 1 who was given co-trimoxazole alone (fig 2). All patients required operation in the active stage. The indications for operation were acute left ventricular failure and pulmonary oedema secondary to severe aortic regurgitation in three patients, and fear of embolism in one patient with a previous embolic cerebrovascular accident and echocardiographic evidence of a pedunculated, freely mobile vegetation dangling into the left ventricular outflow tract.

At operation all patients had aortic valve vegetations. Three patients (cases 1, 2, and 4) had a cusp perforation. Two patients (2 and 4) had a detached leaflet. Patient 3 had an aortic root abscess. The patient in whom the mitral valve was affected had a vegetation with tear on the anterior leaflet of the mitral valve and ruptured chordae tendineae.

Histopathology showed inflammatory cell infiltration in all cases and Gram negative bacilli. *Brucella* was grown from samples taken from patients 1 and 2, but biotyping was not performed because *Br melitensis* is the most common cause of brucellosis in Saudi Arabia.

All patients had aortic valve replacement and patient 4 also had mitral valve replacement. The aortic valves were replaced with the following prostheses: Smeloff-Cutler in patient 1, Saint Jude in 2 and 3, and Björk-Shiley in 4. The mitral valve was replaced with a Björk-Shiley prosthesis. There were no operative deaths. One patient (case 2) needed intra-aortic balloon support postoperatively and had a perioperative haemorrhagic cerebrovascular accident.

POSTOPERATIVE FOLLOW UP

In all patients *Brucella* titres, blood cultures, and echocardiography were repeated every three months for a year. Three months after operation all *Brucella* titres had dropped markedly except in patient 2 who had only one dilutional decrease. All showed further decreases at nine and twelve months (fig 2).

At follow up no patient had positive blood cultures or evidence of vegetations by echocardiography.

All patients continued their preoperative antibiotics (co-trimoxazole and rifampicin) for six months after operation except patient 2 who had an additional three months' treatment because of a delayed drop in *Brucella* titre. During follow up (mean 15 months) there was no recurrence.

Discussion

Brucella endocarditis is the most common cause of death in human brucellosis. Peery and Belter found endocarditis in 80% and myocardial abscess in 43% of a series of 44 necropsies on cases of fatal brucellosis.⁶ Dalrymple-Champneys observed only five cases of endocarditis among 1500 cases of human brucellosis in England over a period of 43 years¹³; Spink reported four cases in a series of 244 patients in the United States.¹⁴ This low incidence of endocarditis in the West is not surprising as most of the cases were caused by *Br abortus*, a species known to cause mild disease with uncommon suppurative or disabling complications.^{15 16} Endocarditis may be a more common complication of systemic brucellosis

in countries where there is a high prevalence of *Br melitensis* and rheumatic heart disease since *Br melitensis* is known to cause more severe, acute disease associated with disabling complications.¹⁵⁻¹⁷ In a review of endocarditis at King Faisal Specialist Hospital, *Brucella* endocarditis was seen in 8.5% of patients treated for endocarditis.¹⁸

As in previous reports of *Brucella* endocarditis, all our patients were men with a history of ingesting fresh, raw milk, and all had symptoms for at least three months before presentation.^{7-12, 19, 20}

Review of published reports indicates that the aortic valve is affected in 75% of cases, and the mitral valve, mitral and aortic valves, and prosthetic valves are equally affected in 8.3% of cases. In three of our patients the aortic valve was affected and in the fourth both the aortic and mitral valves were affected.

Diagnosis of endocarditis in a course of brucellosis is difficult. A changing heart murmur, high *Brucella* titre, and echocardiography are helpful. A changing heart murmur with haemodynamic deterioration was seen in two of our patients while they were in hospital, and one patient was admitted with severe aortic regurgitation and pulmonary oedema. This also accords with other reports.²⁰

The *Brucella* titre was very high (≥ 2560) in all our patients and it remained high or increased until operation. This relatively high *Brucella* titre in a course of *Brucella* endocarditis has been reported by Cohen *et al.*²⁰

Echocardiography, by showing bulky vegetations in all four patients, was very helpful in establishing the diagnosis of endocarditis. In three patients premature closing of the mitral valve indicated aortic regurgitation.

Blood cultures were positive in only one patient. This low yield of blood cultures may be because of the fastidiousness of the organism, previous antibiotic treatment, and the long interval between onset of symptoms and diagnosis.⁴

Brucella endocarditis usually has an unremitting and fatal course with death occurring within three to eleven months of the onset of symptoms,¹⁹ and usually from congestive heart failure. Cure with antimicrobial treatment alone^{4, 20-22} has been reported only in two doubtful cases with mixed bacterial endocarditis.^{23, 24} We elected to treat the patients in our institution with co-trimoxazole and rifampicin because rifampicin has been shown to be active against *Br melitensis*,^{25, 26} and co-trimoxazole is clinically effective against brucellosis.²⁷⁻³¹ All our patients needed operation in the active stage, however: three because of acute pulmonary oedema secondary to aortic valve destruction and the fourth because of fear of further embolic episodes. At oper-

ation all patients showed evidence of active disease.

Operation for *Brucella* endocarditis was reported in 1967 by Ehrenhaft, who replaced an infected aortic valve. The prosthetic valve became infected and the patient died after 38 days.³² There are six reported cases of surgically cured *Brucella* endocarditis⁷⁻¹²: in five the aortic valve was affected and the sixth had an infected prosthetic (Starr-Edwards) mitral valve. All the five reported cases with aortic valve replacement had one to three months' antibiotic treatment after operation and the patient with an infected prosthetic mitral valve was treated for one year. Our patients had six months' treatment with co-trimoxazole and rifampicin after operation, and one had a further three months' treatment mainly because of delayed fall in *Brucella* titre (fig 2). There is no indication in published reports of how long antibiotic treatment should be continued after operation; however, six months seems to be adequate if the *Brucella* titre is falling. There was no evidence of recurrence of infection in any of our patients in more than 15 months' follow up.

References

- 1 Havas L. Problems and new developments in the treatment of acute and chronic brucellosis in man. *Acta Trop (Basel)* 1980;37:281-6.
- 2 Young EJ. Human brucellosis. *Rev Infect Dis* 1983;5:821-42.
- 3 Wise RI. Brucellosis in the United States, past, present and future. *JAMA* 1980;244:2318-22.
- 4 Salata RA, Ravdin JI. Brucellosis species (brucellosis). In: Mandell GL, Douglas RD, Bennett JE, eds. *Principles and practice of infectious diseases*. New York: John Wiley, 1985:1283-90.
- 5 Buchanan TM, Faber LC, Feldman RA. Brucellosis in the United States 1960-1972. An abattoir-associated disease. Part I. Clinical features and therapy. *Medicine (Baltimore)* 1974;53:403-13.
- 6 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.
- 7 Wolf LM, Hazan E, Letac B, *et al.* Endocardite brucellienne. Guérison per remplacement valvulaire en periode evolutive. *Nouv Presse Med* 1973;2:493-5.
- 8 O'Meara JB, Eykyn S, Jenkins BS, *et al.* *Brucella melitensis* endocarditis: successful treatment of an infected prosthetic mitral valve. *Thorax* 1974;29:377-81.
- 9 Cleveland JC, Suchor RJ, Dague J. Destructive aortic valve endocarditis from *Brucella abortus*: survival with emergency aortic valve replacement. *Thorax* 1978;33:616-8.
- 10 Pratt DS, Tenney JH, Bjork CM, Reller LB. Successful treatment of *Brucella melitensis* endocarditis. *Am J Med* 1978;64:897-900.
- 11 Paxderka E, Jones JW. *Brucella abortus* endocarditis: successful treatment of an infected aortic valve. *Arch Intern Med* 1982;142:1567-8.

- 12 Heibig J, Beall A, Myers R, *et al.* Brucella aortic endocarditis corrected by prosthetic valve replacement. *Am Heart J* 1983;106:594-6.
- 13 Dalrymple-Champneys W. *Brucella infection and undulant fever in man.* London: Oxford University Press, 1960:1.
- 14 Spink WW. *The nature of brucellosis.* Minneapolis: University of Minnesota Press, 1956:145-90.
- 15 Spink WW. Some biologic and clinical problems related to intracellular parasitism in brucellosis. *N Engl J Med* 1952;247:603-10.
- 16 Spink WW. Host parasite relationship in brucellosis. *Lancet* 1964;ii:161-4.
- 17 Williams E. Brucellosis. *Practitioner* 1982;226:1507.
- 18 Halim M, Jeroudi M, Mercer E, *et al.* Infective endocarditis in King Faisal Specialist Hospital, review of 35 consecutive adult patients. *Annals of Saudi Medicine* 1986;6:179-83.
- 19 Hart FD, Morgan A, Lacey B. *Brucella abortus* endocarditis. *Br Med J* 1951;i:1048-53.
- 20 Cohen PS, Maguire JH, Weinstein L. Infective endocarditis caused by gram negative bacteria: a review of the literature 1945-1977. *Prog Cardiovasc Dis* 1980;22:205-42.
- 21 Buchanan TM, Petersdorf RG. Brucellosis. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's principles of internal medicine.* 10th ed. New York: McGraw-Hill, 1983:974-6.
- 22 Williams E. Brucellosis. In: Wetherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford textbook of medicine.* Oxford/London: Oxford University Press, 1983:5.221-6.
- 23 Quinn RW, Brown JW. Bacterial endocarditis. *Arch Intern Med* 1954;94:629-48.
- 24 Hudson RA. *Brucella abortus* endocarditis: a case. *Circulation* 1957;16:411-13.
- 25 Llorens-Terol J, Busquets RM. Brucellosis treated with rifampicin. *Arch Dis Child* 1980;55:486-8.
- 26 Binda G, Domenichini E, Gottardi A, *et al.* Rifampicin, a general review. *Arzneimittelforschung* 1971;21:1907-77.
- 27 Dendikos GK, Papolyzos N, Marketos N, *et al.* Trimethoprim and sulfamethoxazole in brucellosis. *J Infect Dis* 1973;128(S):S731-3.
- 28 Lal S, Modawal KK, Fowle AS, *et al.* Acute brucellosis treated with trimethoprim and sulphamethoxazole. *Br Med J* 1970;iii:256-7.
- 29 Hassan A, Erian MM, Farid Z, *et al.* Trimethoprim-sulphamethoxazole in acute brucellosis. *Br Med J* 1971;iii:159-60.
- 30 Gunchi G, de Rose F, Fabini F. Treatment of brucellosis with trimethoprim-sulfamethoxazole. *Chemotherapy* 1971;16:332-5.
- 31 Lifeso RM, Harder E, McCorkell SJ. Spinal brucellosis. *J Bone Joint Surg [Br]* 1985;67:345-51.
- 32 Ehrenhaft JL. In discussion of a paper by Kasier GC, Willman VL, Thurmann M, Hanlon CR. Valve replacement in cases of aortic insufficiency due to active endocarditis. *J Thorac Surg* 1967;54:491.