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A Review of *Brucella endocarditis*

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Abstract

Brucella endocarditis is one of the rare, life-threatening complications of a multisystemic zoonotic disease, brucellosis. Careful history taking, clinical examinations, and detailed laboratory tests with special culture media in endemic zones help in diagnosis of this latent disease. No consensus on the exact management of this disease has reached till now. Hence, both medical management and surgical interventions in selective cases were the treatment of choice. This article provides a review of the earlier literature on *Brucella endocarditis*.

Keywords

- Brucellosis
- endocarditis
- multimodality approach
- combined management

Introduction

Brucellosis is a quiet challenging zoonotic disease caused by an aerobic gram-negative uncapsulated intracellular coccobacilli *Brucella*, with three species (*B. melitensis, B. abortus*, *B. suis*)[1] (►**Fig. 1**). It is mainly transmitted via unpasteurized dairy products, inhalation of contaminated aerosols, or contact with infected secretions. Because of its use in bioterrorism,[2] it gathered more attention in recent years. In the present era of immunosuppression due to post-coronavirus disease 2019 illness, steroid abuse, there is every chance of resurgence of these illnesses. The key points of *Brucella endocarditis* (BE) were mentioned in ►**Table 1**.

Incidence and Prevalence

Brucellosis affects both adults and children and remains a major health problem in many developing regions.[3,4] According to the World Health Organization (WHO), 500,000 new brucellosis cases are reported each year with a prevalence of more than 10/100,000 population noted in endemic countries.[5] The Middle East is the most common endemic zone for brucellosis with high prevalence in Mediterranean, Mexico, and South America. Way back in 1960, Peery and Belter[6] in a necropsy study found endocarditis in 80% and abscess in 45% of total brucellosis. Osteoarticular system (25–30%) is most commonly affected followed by genitourinary, central nervous system, and cardiovascular system. Though the cardiovascular involvement is <2% causing endocarditis, it accounts for the main cause of mortality.[1] In a series of 1,500 cases of human brucellosis, there were only five cases (0.3%) of endocarditis,[7,8] yet another recent study reported 4% of endocarditis.[9] The disease is rare in western countries where the agent is *B. abortus*, which causes mild disease.[10]

It is more common in men than women.[11] Most common human brucellosis is caused by *B. melitensis* that is known to cause more severe, acute disease associated with more complications.[10] Since 2000 western central China and Tibet had shown increased endemicity.[1] In countries where brucellosis is an endemic zoonosis and the rheumatic heart disease prevalence is high, BE is of more common occurrence.

The incidence of BE in various studies is mentioned in ►**Table 2**.[12]

Clinical Presentation

Brucellosis has three presentations: acute (<2 months), subacute (2–12 months), and chronic forms. The involvement is a multisystem disease that may vary from mild to fulminant

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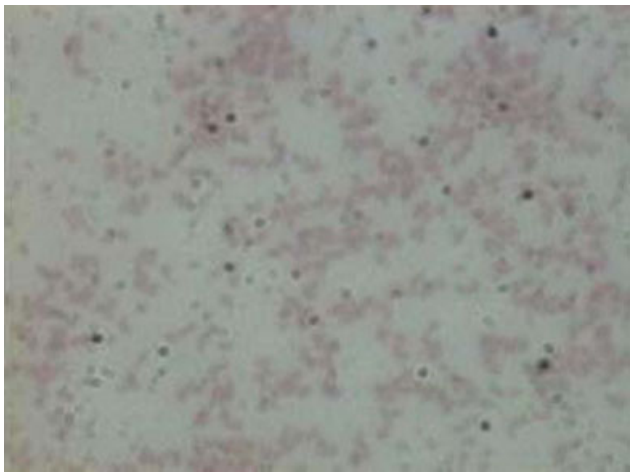

Fig. 1 Gram's smear of culture showing gram negative *Brucella melitensis bacillus*.

Table 1 Key points about *Brucella* endocarditis

Key Points to remember
• High index of suspicion is required for the diagnosis of *Brucella endocarditis* ◦ In an endemic area ◦ Contact with livestock ◦ Culture negative endocarditis
• Careful examination is needed to pick up the signs and symptoms of early features of endocarditis in brucellosis
• Need to take the help of multiple investigations for the diagnosis of this latent organism
• Surgery is reserved for selective cases of refractory heart failure
• Combined medical and surgical treatment is needed to decrease the morbidity and mortality

course with 30 to 40% morbidity. The most common manifestations are undulant fever, arthralgia, asthenia, hepatosplenomegaly, and other constitutional symptoms. The incubation period is ~2 to 6 weeks but may occasionally be much longer. The patients with BE suffer for 6 to 12 months. Among the cardiac complications associated with endocarditis are paravalvular leakage, ring abscess, congenital heart disease (ventricular septal defect), rheumatic heart disease, and acute valve malfunction. Extracardiac manifestations such as sepsis, septic shock, renal failure, pneumonia, disseminated pulmonary abscess, liver abscess, sacroiliitis, and encephalopathy were reported.[13]

Coming to the cardiac involvement, the frequently infected native valve is aortic valve (29–75%) followed by the mitral valve. Secondary infection of predamaged mitral valve is more common than the aortic valve.[14] Prosthetic valves were affected in 8.3% of cases.[11,15] The most frequent cardiac symptoms are dyspnea due to congestive heart failure (CHF) (75–90%). The presence of new onset murmur is the most common clinical sign.[16] The occurrence of embolic manifestations was not more common than endocarditis caused by other organisms.[17,18]

Diagnosis

Definitive diagnosis of BE is made in accordance with Duke's criteria. High degree of suspicion is needed for diagnosis in a patient living in endemic region and is in contact with livestock and veterinary products. Multi modality approach including Brucella endocarditis blood culture, echocardiography (transthoracic/transesophageal), and serology help in diagnosing this latent disease. Other tests like immunohistology, polymerase chain reaction (PCR), and analysis of surgical material also aid in diagnosis.

Blood Culture

Three sets of blood cultures should be drawn half an hour apart from different areas. Though it is the gold standard for diagnosis of *Brucella*, it has a low diagnostic yield due to its fastidious growth and requirement of suitable culture medium and previous usage of antibiotics. The sensitivity of blood culture is low (15–20%), but the specificity is higher.[19] It depends on culture media used, stage of disease, previous antibiotic use, and technique of culture. Hence, BE is associated with higher rate of negative blood cultures. It is advisable from literature review that BE should be looked for in culture-negative endocarditis. While positivity of blood culture in *Brucella* infection is 15 to 70%, in BE it is above 80%.[20,21] In a report by Reguera et al, the positive rate is 63.6% when culture was processed in absence of previous antibiotic therapy,

Table 2 Incidence of *Brucella endocarditis* in various studies

Sl. no.	Year of study	Author	Incidence of *Brucella endocarditis* in patients
1	1956	Spink[10]	1.6% (4/244)
2	1960	Dalrymple-Champneys [8]	0.3% (5/1500)
3	1960 (necropsy study)	Peery and Belter[6]	80% in 44 cases
4	1986	Halim et al[7]	8.5%
5	2011	Calik and Gokengin[12]	51/4204 (brucellosis cases)
6	1989	Colmenero et al[38]	1.1% (6/530 cases)
7	2002	Aygen et al[9]	0.4% (2/480 cases)
8	2016	Du and Wang[49]	3% (5/189)

whereas Esmailpour et al[22] showed 22.2% positivity rate. Culture can be positive in 40 to 90% of acute and 5 to 20% of chronic cases. However, the recent use of automated culture systems has led to more early identification of *Brucella* species.[23] Mean duration of symptoms before the diagnosis of prosthetic valve endocarditis was also prolonged in patients with a history of brucellosis.[24]

Serology

These are more sensitive than blood culture but less specific. The diagnostic role of serology in the diagnosis of *Brucellosis* is very crucial.[25] The various tests used are enzyme-linked immunosorbent assay (ELISA), immunofluorescence, reverse immunofluorescence, Rose Bengal test, with ELISA having highest sensitivity and specificity.[21] Wright agglutination and Rose Bengal test serve as sensitive diagnostic tools. But these tests can give false negative results in early stages. Wright seroagglutination >1/160 or a Coombs anti-Brucella test > 1/320 and an indirect immunofluorescence >1/512 are considered as significant titers.[26,27] The recurrence of the disease can be diagnosed by 2-mercaptoethanol Wright test. Because of its low specificity, these tests should be interpreted with caution in highly endemic areas. Molecular testing by PCR had both high sensitivity and high specificity.

Echocardiography[28]

Transthoracic echocardiogram plays an important role in identifying the structural damage but transesophageal echocardiogram is often required in many cases. Bulky vegetations on the valves, abscess, and ulcerations are the most common features.[29] Valvular regurgitation (aortic/mitral) is acute in nature, and cardiac fistulas are also commonly known to occur, but any structural element can be affected. There is one report of rupture of aortic cusp. In prosthetic valve endocarditis, the most common complications were bulky vegetation, paravalvular leakage, aneurysm, abscess, and valve malfunction.[30,31] Echocardiographic features are summarized in ►**Table 3**.

Table 3 Echocardiographic features of *Brucella* endocarditis

Echocardiographic features
Native valve Aortic valve—Most common affected valve Bulky vegetations on valvular leaflets (>0.5–1.0cm) Valvular regurgitation Premature closure of mitral valve with acute severe aortic regurgitation Rupture of cusps Valve abscess Root abscess Cardiac fistulas
Prosthetic valve Bulky vegetations Paravalvular leak Aneurysm Abscess Valve malfunction

Electrocardiography

Electrocardiographic changes may reflect involvement of the cardiac conduction system, that is, right or left bundle blocks or atrioventricular blocks.

An algorithm for the management of BE is mentioned by Raju et al.[32]

Treatment

BE has an unremitting and fatal course with mortality occurring within 3.11 months usually with CHF. Antibiotic therapy and surgical intervention were the mainstays of treatment.

Antibiotic Treatment

There is some uncertainty pertaining to the appropriate course and duration of various drugs used in the treatment. Its intracellular nature paves a challenge for most of the antibiotic regimens.[33] Hence, no clear evidence on choice of antibiotics, but those with good penetration of cellular walls of macrophage and with bactericidal effects should be of primary choice. The most commonly prevailing regimen is the combination of doxycycline (200 mg) and rifampicin (600–900mg) for 10 to 12 weeks with an aminoglycoside coverage for initial 2 to 4 weeks.[34] Other drugs that have shown some promising evidence and lower recurrence rates are cotrimoxazole, quinolones, in combination with doxycyclin.[35] However, the European society[36] suggests doxycycline + cotrimoxazole + rifampin orally for more than 3 months. The WHO[37] recommends combination of streptomycin and tetracycline, but it has 15 to 40% of recurrence rate.[38] The earlier the initiation of antibiotic regimen, the better will be the outcome.[39]

Surgical Intervention

Because of its high degree of tissue destruction, early surgical intervention with valve replacement gained lot of momentum in initial days of management. Wolf et al[40] reported first surgical intervention for aortic valve endocarditis in 1967. A review of 308 cases by Keshtkar-Jahromi et al showed surgical intervention improved the clinical outcome. The mortality was 6.7% in combined surgical and medical group as against 32.7% in medical treatment alone with $p < 0.001$.

But Cohen et al[41] observed similar outcomes with conservative and surgical intervention in patients with no significant valve damage and heart failure. Hence, surgery is reserved for massive valve damage with persistent CHF despite appropriate medical therapy. The main aim of surgery is the removal of infected material, affected valves, and if needed radical excision. Duran et al[42] had suggested vegetectomy in patients with single vegetation. In a systematic review, relapse of brucellosis after an appropriate treatment was recorded in five patients.[43]

Postoperative use of antibiotics was studied by many workers[44,45] and it is advised to continue antibiotic coverage for at least 6 months to prevent the relapses that can be assessed by Wright serologic titer.[46]

To summarize, a combination of both medical and surgical intervention is needed for BE, which includes pre- and

Table 4 Combined management of *Brucella* endocarditis

Medical management Doxycycline (200 mg) and rifampicin (600–900mg) for 10–12 weeks With an aminoglycosides coverage for initial 2–4 weeks Lower recurrence rates are with cotrimoxazole, quinolones, in combination with doxycycline Others—streptomycin and tetracycline
Surgical management Indications Massive valve damage Persistent CHF despite medical management Removal of infected material Valve replacement Vegetectomy
Combined medical and surgical treatment Preoperative and postoperative appropriate antibiotic coverage with timely surgery

Abbreviation: CHF, congestive heart failure.
Treatment options for *Brucella endocarditis*.

postoperative coverage of antibiotics in patient who are benefited from surgical therapy.[47,48] The synopsis of the treatment of BE is mentioned in ►**Table 4**.

Prognosis

Though the mortality of brucellosis is low, the endocarditis accounts for 80% of the mortality related to it.[6] CHF is responsible for majority of deaths due to BE.

This has not been previously published or submitted elsewhere for publication.

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This manuscript highlights the importance of zoonotic diseases and the need of high index of suspicion for the diagnosis of this latent infection.

Conflicts of Interest
None

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