

Clinical Characteristics and Outcome of Brucella Endocarditis: A Case Series

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Purpose: Brucella endocarditis is a rare complication with a high mortality risk. This research aims to evaluate patients diagnosed with Brucella Endocarditis and review clinical characteristics, diagnosis, and treatment strategies to serve as a foundation for future research in managing Brucella endocarditis and improving patient care and outcomes.

Patients and Methods: This retrospective study reviewed the medical records of patients diagnosed with Brucella endocarditis from 2011 to 2022. The study included patients of all ages and genders who were diagnosed based on positive serum serology or blood culture in conjunction with clinical presentation. Diagnostic criteria for endocarditis were based on evidence of endocardial involvement, as confirmed by echocardiographic findings consistent with infective endocarditis. Descriptive statistics were used for data analysis.

Results: Nine patients were included in this study. The most common presenting symptom was shortness of breath. Treatment regimens included Doxycycline and Rifampicin, always in combination with other antibiotics. Surgical intervention was necessary for two-thirds of the patients. Complications, such as septic shock, stroke, and heart failure, were observed in most cases. Six patients achieved clinical and microbiological cures, while one-third of the patients died. The deaths were primarily attributed to patients being deemed unsuitable for surgery due to a high surgical risk, based on their comorbidities and clinical assessments.

Conclusion: This study highlights the importance of initiating an appropriate antibiotic regimen in a timely manner. Particularly in patients with pre-existing heart diseases, surgical intervention can significantly improve patient outcomes and reduce complications associated with Brucella endocarditis.

Keywords: brucellosis, *Brucella* endocarditis, *Brucella* complication, Saudi Arabia

Introduction

Brucellosis is an infectious zoonotic disease that is transmittable to humans.¹ The causative organism is a gram-negative intracellular $\alpha 2$ proteobacteria bacillus of the genus *Brucella*.² The three primary mechanisms of transmission include inhalation of contaminated aerosols, close contact with infected farm animals, and consuming unpasteurized dairy products.³ After the infection, bacteria spread via the lymph nodes and macrophages to other organs such as the liver, bone marrow, spleen, and reproductive organs.⁴ It can cause chronic diseases such as meningitis, spondylitis, endocarditis, and arthritis.⁵ Globally, there is a comprehensive regional variation regarding the reported incidence of brucellosis.⁶ The Middle East, Africa, the Mediterranean Basin, Central Asia, and Latin America are endemic areas of brucellosis.⁴ According to recent epidemiology data from 2020, brucellosis has the third highest reported cases of notifiable communicable diseases in Saudi Arabia. Riyadh recorded the highest number of cases (492 cases, accounting for 19.34%), with the majority of cases affecting the 15–45 age group (57%).⁷

Brucella infections can present with a wide range of clinical symptoms.¹ Although it most commonly affects the osteoarticular and genitourinary systems, rare cardiovascular complications carry the highest fatality rates in brucellosis.^{1,8} Based on the literature, it accounts for approximately 0.8–5% of all cases with life-threatening effects of up to 80% mortality rate of Brucella endocarditis reported cases.^{9,10} Cardiovascular complications include pericarditis, myocarditis, and endocarditis.⁸ Infective endocarditis is described as an infection of a native or a prosthetic heart valve, the surface of the endocardium, or a cardiac device implanted in the patient.⁴ The predominant lesion that is involved in Brucella endocarditis is aortic insufficiency, which can lead to serious morbidity and mortality due to the causative calcifications and fibrosis of the valves.¹¹ Brucella endocarditis presents as prolonged fever, the most common symptom, and a history of close contact with an infected farm animal or intake of unpasteurized dairy products. Furthermore, the presence of vegetation on the valves on echocardiography combined with a positive culture is diagnostic.¹² The choice of regimen recommended for brucellosis is individualized based on the patient's characteristics and the disease localization. For endocarditis and other major organ involvement, a combination of antibiotics, including aminoglycosides, is recommended.¹³ Surgical therapy is also highly recommended for source control to avoid failure of therapy or disease relapse. Surgery improves outcomes by directly eradicating the infected heart tissue and vegetation.¹⁴

The high mortality rate could be attributed to delayed diagnosis due to the clinical presentation, diagnosis challenges, and other mimickers of *Brucella* endocarditis.^{4,15} Furthermore, rare cases of multivisceral involvement, such as severe acute pancreatitis, have been reported, demonstrating the complexity of the disease's manifestations.¹⁶ Given the limited number of local studies on Brucella endocarditis, this tertiary center study aimed to assess its clinical characteristics and outcomes.

This study retrospectively reviews and evaluates the clinical characteristics and outcomes of patients diagnosed with Brucella endocarditis at King Abdulaziz Medical City in Riyadh over the past decade. The findings aim to provide a foundation for future research and contribute to improved management strategies for this rare but serious condition.

Methods

A descriptive, retrospective systemic record review was conducted for patients diagnosed with Brucella endocarditis between January 2011 and December 2022. Diagnosis was based on a positive serology (Brucella antibody titer $\geq 1:160$ by standard tube agglutination test), molecular testing, or blood culture, in combination with echocardiographic evidence of infective endocarditis. Patients were identified through the Electronic Medical Record system (BESTCare) at King Abdulaziz Medical City in Riyadh. The study included patients of all ages (adults and pediatrics), genders and nationalities diagnosed with infective endocarditis secondary to brucellosis.

Patients without confirmatory laboratory tests or without echocardiographic evidence of endocarditis were excluded. Those meeting the inclusion criteria were selected using a non-probability consecutive sampling technique. Screening was performed through microbiology and serology labs and patients with positive results for Brucella were assessed for infective endocarditis using echocardiography reports.

Data collected included demographics, clinical profile, laboratory profile, treatment regimens, and outcomes. Demographics included age, gender, nationality, comorbidities, smoking status, and admission/discharge dates. Clinical and epidemiological profile variables included risk factors (eg, consumption of unpasteurized milk, exposure to farm animals), presenting symptoms such as fever, malaise, back pain, dyspnea, and chest pain, valve involvement, and extracardiac complications. The laboratory data included *Brucella* serology, blood culture, surgical specimens cultures, and *Brucella* PCR results. Basic workups, such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein test (CRP), procalcitonin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine clearance test (CrCl), were included. Treatment variables included surgical intervention and the antibiotic regimen, including: (doxycycline, ciprofloxacin, gentamicin, streptomycin, trimethoprim/sulfamethoxazole (TRM/SMX), and Rifampin). The variables for the outcomes were mortality, heart failure, chronic kidney disease, and complete recovery. Outcome variables focused on clinical cure, complications, and mortality.

Data entry was performed using Excel, and descriptive statistics were employed to analyze the data. Mean, median, and standard deviation were calculated for all numerical variables, for example, age, and frequencies for categorical variables. The sample size reflects the number of available cases meeting the criteria and is not a source of bias, as the

study focuses on clinical outcomes. This study was approved by the Institutional Review Board (IRB) in the Ministry of National Guard Health Affairs under Project N. (SP22R-093-05) at King Abdullah International Medical Research Center.

Results

Out of 1044 confirmed Brucellosis infections, nine patients were confirmed to have *Brucella* endocarditis. Eight out of the nine were male patients, and two of them were children (10 and 11 years old). Of all patients, five confirmed a previous history of unpasteurized milk ingestion. Regarding underlying heart diseases, eight patients were previously diagnosed with heart disease. In all of these eight patients, valvular disease was found. The most common presenting symptom was shortness of breath, seen in nine (66%) of our patients. Followed by fever and fatiguability, accounting for (55%) five of the patients. 4 out of 9 patients complained of chest Pain. Three patients complained of unexplained weight loss, and two had coughs. Abdominal pain, back pain, myalgia, and vomiting were documented once in three distinct patients. Six patients had aortic valve involvement with no other valves affected. Three patients had vegetations found on a previously inserted Implantable-cardioverter-defibrillator (ICD) lead in the right atrium. Seven patients (77%) had positive titer levels for both *Brucella melitensis* and *Brucella abortus* (greater than 1:160). Blood cultures were positive for all nine patients at the time of diagnosis. (Table 1).

All the antibiotic regimens used for our patients included Doxycycline and Rifampicin. All patients received a minimum of three agents to treat brucellosis. Trimethoprim/sulfamethoxazole was the most common additional drug used with doxycycline and rifampicin in six patients, followed by ciprofloxacin (5 patients), Aminoglycoside (streptomycin or gentamicin for 4 patients) and ceftriaxone in one patient. Six patients underwent cardiac surgical intervention during their admission. Perioperative findings varied among cases, with some showing significantly damaged valves and others displaying infected-looking tissues as described by the operating surgeon. The shortest stay in the hospital was 28 days, and the most extended stay was 104 days (average hospital stay around 58 days). Seven out of the nine patients had complications. The most common complications were septic shock, stroke, and heart failure; for further details, refer to Table 2.

Regarding the patients' outcomes, six patients reached clinical and microbiological cures after the completion of their treatment course. Unfortunately, three patients died, and two of those were treated conservatively with antibiotics alone. The timing of death after their diagnosis was variable, ranging from 70 days to 90 days and 197 days. One patient suffered from Disseminated intravascular coagulation (DIC), septic shock, and fatal arrhythmias two months after admission. The other patient suffered from recurrent strokes due to other comorbidities and subsequent acute deterioration two months after discharge. The last patient died of an unknown direct cause four months after discharge (Table 2).

Discussion

Although *Brucella* endocarditis (BE) is a rare complication of brucellosis, it carries a high mortality risk, accounting for up to 80% of fatal cases in brucellosis.² In this retrospective study, the median age at presentation was 47 years, which is consistent with the findings in similar studies, with two outlier pediatric cases. Male gender predominance in BE was observed, with only one female patient, which aligns with reports from other studies. Brucellosis is mainly transmitted to humans through direct contact with animals or by consuming unpasteurized animal products.¹⁷

In this study, not all patients had identifiable risk factors, such as consumption of unpasteurized milk or reports of close contact with farm animals. Our findings regarding risk factors are slightly lower than those reported in local studies, although consistent with international data.^{4,13} This may be due to the study's retrospective nature, where it is expected to have missing data. All patients in our study had identifiable cardiovascular risk factors prior to the diagnosis of *Brucella* endocarditis, including pre-existing structural heart disease or variations of valvular heart disease. These conditions are well-established determinants for the development of infective endocarditis, as documented in the literature.^{18,19}

Delay in diagnosis is a significant factor contributing to the severity and mortality of *Brucella* endocarditis. The wide range of nonspecific clinical manifestations often leads to misdiagnosis or late diagnosis, which can result in advanced disease by the time patients receive appropriate treatment.²⁰ In our study, late diagnosis was particularly associated with poorer outcomes, as delayed recognition of the disease allowed complications to progress, leading to fatal consequences

Table 1 Clinical Presentation

Patient	Gender	Age	Raw Milk Ingestion	Symptoms	Duration of symptoms	Underlying valve Disease	Infected valve (ECHO Findings)	Needed TEE	Brucella Melitensis titre	Brucella Abortus Titre	Blood Culture
1	M	35	0	Chest pain and Fever	3 weeks	Aortic valve regurgitation, mitral valve regurgitation	Aortic valve (Dehiscence and paravalvular leak)	0	1:20,480	1:10240	Positive
2	M	50	1	Fever, SOB, Malaise, Abdominal pain	1 week	Rheumatic heart disease, mechanical aortic valve	Aortic valve (Long mobile vegetation with root abscess)	1	1:5120	1:2560	Positive
3	M	63	0	Weight loss, vomiting, chronic cough	1 Month	Tricuspid valve regurgitation, mitral valve regurgitation	Right atrial wall, ICD lead (Multiple large vegetations)	0	1:20,480	1:15120	Positive
4	M	62	1	SOB, Malaise, Chest pain	2 weeks	Mitral and tricuspid valves regurgitation	ICD lead (Large mobile mass)	1	>1:20,480	>1:20480	Positive
5	M	11	0	Fever, Back pain, Muscle weakness	3 Months	Congenital bicuspid aortic valve	Aortic valve (Vegetation and thickened valve)	0	1:2560	1:2560	Positive
6	M	68	1	Fever, Malaise, SOB, Chest pain, Weight loss, Cough	1 Month	Congenital bicuspid aortic valve	Aortic valve (calcified valve vegetations)	1	1:5120	1:640	Positive
7	F	52	0	SOB	2 Days	Mechanical aortic valve	ICD lead (Large mobile masses)	0	Not done	Not done	Positive
8	M	10	1	Fever, SOB, Malaise, Chest pain	1 week	None	Aortic valve (Retro-aortic abscess and vegetations)	0	<1:160	<1:160	Positive
9	M	69	1	SOB, Malaise, Weight loss	20 Days	Aortic prosthetic valve	Aortic valve (vegetation with aortic root abscess)	0	1:280	1:2560	Positive

Abbreviations: TEE, Transesophageal Echocardiogram, SOB, shortness of breath, ICD, Implantable-cardioverter-defibrillator.

Table 2 Treatment and Outcome

Patient Number	Antibiotics	Surgery	Duration of Therapy (Months)	Complications	Outcome
1	Doxycycline, Rifampicin, Ciprofloxacin	Yes	15	Heart failure	Clinical / microbiological cure
2	Doxycycline, Bactrim, Ciprofloxacin, Gentamycin, Rifampicin	None	6	Splenic infarction	Clinical / microbiological cure
3	Doxycycline, Ciprofloxacin, Rifampicin	Yes	9	Infective spondylitis	Clinical / microbiological cure
4	Doxycycline, Gentamicin, Streptomycin, Bactrim, Rifampicin	Yes	1.5	Septic shock, DIC	Death
5	Doxycycline, Gentamycin, Bactrim, Rifampicin, Ciprofloxacin	Yes	1.5	None	Clinical cure
6	Doxycycline, Ciprofloxacin, Rifampicin	Yes	7	None	Clinical / microbiological cure
7	Doxycycline, Rifampicin, Gentamicin, Bactrim	None	3	Septic shock, Stroke	Death
8	Ceftriaxone, Doxycycline, Rifampicin, Bactrim	Yes	4	Heart failure, AKI	Clinical / microbiological cure
9	Rifampicin, Doxycycline, Bactrim	None	2	Cardio-embolic stroke with haemorrhagic transformation	Death

Abbreviations: DI, disseminated intravascular coagulation, AKI, acute kidney injury.

in some cases. The most common clinical features at the time of diagnosis are shortness of breath followed by fever, malaise, and chest pain, respectively. Less common symptoms that were found are weight loss, cough, abdominal pain, and back pain, as in concordance with the results of other studies.²⁰

BE was reported to usually affect the left side of the heart.²¹ The vegetations were found on the aortic valve in 66% of our patients, whereas the remaining 33% were found on the ICD lead. Although it is reported in other studies that can involve the native aortic valve, 50% of patients in our study with vegetations involving the aortic valve had prosthetic aortic valves.^{4,22} Notably, the three patients with native aortic valves included two bicuspid aortic valve congenital defects, and only one patient in our study was free of underlying risk factors.

Although blood culture is considered the gold standard for detecting *Brucella*, its low sensitivity, reported to be between 15%-70%, complicates timely diagnosis. Serological testing, combined with clinical assessment, has become increasingly important for early detection.^{17,20} While blood culture yielded positive results in all patients, serological tests were identified in seven cases only. In our study, the combination of serological or microbiological confirmation with echocardiography findings played a critical role in diagnosing *Brucella* endocarditis. Three patients required transesophageal echocardiography (TEE) to confirm the diagnosis, underscoring the importance of this modality in high-risk patients, particularly those with underlying valvular disease. The reliance on blood culture or transthoracic echocardiogram alone in some cases may have contributed to delays in diagnosis, highlighting the need for combining multiple diagnostic tools to ensure timely detection.

The treatment of *Brucella* endocarditis typically involves prolonged antibiotic therapy, often in combination with surgical intervention. Surgical intervention is crucial for patients with significant valvular involvement or other complications such as abscesses or pseudoaneurysms. Intervention timing and infection severity are the significant determinants of outcomes. The decision to perform surgery depends on factors such as vegetation size and location, valvular dysfunction severity, heart failure presence, and the patient's overall condition and surgical tolerance. It stresses that *Brucella* endocarditis is a severe life-threatening condition requiring a multidisciplinary approach for favourable outcomes. In our cohort, two patients were not suitable for surgery due to high surgical risk from comorbidities, which contributed to their poor prognosis and eventual death. This highlights the importance of early surgical assessment to improve patient outcomes. One patient who underwent both medical and surgical treatment died due to septic shock and disseminated intravascular coagulation (DIC) after prolonged hospitalization.

Late deaths in our study were primarily associated with advanced disease at the time of diagnosis and the inability to undergo surgical intervention due to poor clinical condition. In the context of *Brucella* endocarditis, these outcomes can be linked to the disease's hallmark complications, such as progressive valvular destruction, heart failure, and septicemia, which are well-documented in the literature as leading causes of mortality in BE. The persistence of infection, along with delayed diagnosis and treatment, likely worsened the patients' conditions, making recovery more difficult. In these cases, it is plausible that the disease progression directly contributed to the inability to perform surgical intervention, ultimately leading to poor outcomes.

The antibiotic regimens used in this study were consistent with current evidence-based practices, with rifampicin and doxycycline forming the backbone of treatment in all cases. Additional antibiotics, such as trimethoprim/sulfamethoxazole, ciprofloxacin, and gentamicin, were used as part of combination therapy. In some cases, 3rd generation cephalosporins were added to address specific postoperative needs.^{13,23} While antimicrobial treatment alone was insufficient for most patients, one patient was successfully treated with antibiotics alone, despite having a prosthetic aortic valve. Gentamicin has often been preferred over streptomycin in the treatment of brucellosis due to its shorter duration of intramuscular injections, offering advantages in terms of cost, ease of administration, and reduced toxicity.^{13,24,25} Additionally, some studies in the literature recommend using a third-generation cephalosporin, rather than aminoglycosides, alongside tetracycline and rifampicin in the treatment of *Brucella* prosthetic valve endocarditis.^{14,20} Several factors have been shown to contribute to improved outcomes, which are consistent with our findings. These include positive blood cultures as a protective indicator, the diagnosis of brucellosis before the onset of endocarditis, early surgical intervention with preoperative antibiotic therapy, and early monitoring for heart failure.¹⁴

Brucella endocarditis remains a life-threatening condition that requires aggressive treatment and long-term follow-up to prevent recurrence. In this study, septic shock accounted for two deaths, while another patient died of unexplored

causes post-discharge. The variability in patient outcomes underscores the complexity of treating BE and the need for individualized treatment plans based on disease severity, patient comorbidities, and the timing of intervention.

While brucellosis is one of the most common communicable diseases in Saudi Arabia, *Brucella* endocarditis is a relatively uncommon condition. This rarity leads to several limitations to this study that are difficult to overcome. Limitations include the small sample size, which limits generalizability, and the retrospective nature, which introduces the potential for missing or incomplete data. Also, the nonspecific symptoms and the limited sensitivity of echocardiographic findings may have led to misdiagnosis or underestimation of its prevalence, preventing the study from providing a definitive estimate of the disease burden within the population. Despite these limitations, the study adds to the literature on the clinical presentation and therapeutic outcomes of *Brucella* endocarditis, providing valuable insights for future research.

Conclusion

In conclusion, this study highlights the clinical presentation and successful therapeutic strategies for *Brucella* endocarditis, emphasizing the importance of blood culture, serology, and echocardiography for accurate diagnosis. The combination of antibiotics, along with surgical intervention when appropriate, has been shown to improve patient outcomes. This study provides valuable insights into the management of *Brucella* endocarditis and underscores the need for further research to enhance diagnostic accuracy and optimize treatment strategies to improve patient prognosis.

Ethical Approval Statement

This study was conducted in compliance with the principles of the Declaration of Helsinki and approved by the Institutional Review Board (IRB) in the Ministry of National Guard Health Affairs and with Project N. (SP22R/093/05) at King Abdullah International Medical Research Center on 27 July 2022. Due to the retrospective nature of the study and the anonymization of patient data, a waiver of informed consent was granted by the IRB. All patient data were handled with strict confidentiality and care to ensure privacy.

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Disclosure

Conflict of Interest: We authors declare that there is no conflict of interest. There are no personal, financial, non-financial, or other interests that may have influenced the research.

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