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Brucella Prosthetic Valve Endocarditis: A Systematic Review

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Abstract

Objective: *Brucella* prosthetic valve endocarditis is a rare but a life-threatening complication of brucellosis. It remains a diagnostic challenge. Optimal treatment of *Brucella* prosthetic valve endocarditis is debated. Available data is limited to case reports or small case series. The purpose of this study was to systematically review all published cases of *Brucella* prosthetic valve endocarditis in the literature.

Method: A systematic review of PubMed database, Google, Google Scholar, and Scopus (From January 1974 to the present) for studies providing epidemiological, clinical and microbiological data as well as data on treatment and outcomes of *Brucella* prosthetic valve endocarditis was performed.

Results: A total of 51 reported cases were reviewed. *Brucella melitensis* (45%) and *Brucella abortus* (11.7%) were the most frequently isolated species. Most common type of prosthesis valve was mechanical prosthesis (84.3%) and ten patients had double valve prosthesis (19.6%). Fever and dyspnea were present in 100% and 37.2% of the cases, respectively. The diagnosis was set with echocardiographic finding in 30 cases (93.7%), which revealed vegetation in 27 cases (84.3%). Most used antibiotics were rifampicin, doxycycline and aminoglycoside or cotrimoxazole. No deaths were noted in patients treated by combined medical and surgical treatment, but mortality was noted in 27.7% of the cases treated by antibiotics alone ($p = 0.006$).

Conclusion: This systematic review highlights diagnostic challenges and demonstrates that surgery improved outcome by reducing mortality in patients treated with the combined surgical and medical treatment option. Brucellosis should be considered in the differential diagnosis of prosthetic valve endocarditis in patients residing in or traveling to areas of endemicity.

Keywords: *Brucella*, Endocarditis, Prosthetic valve, Antibiotics, Surgery

1. Introduction

Human brucellosis is a severe multisystemic disease that may affect any organ. Focal complications, therapeutic failure, and relapse might occur. Cardiovascular complications are rare, among which endocarditis is the most common cardiovascular involvement of the disease [1]. It accounts for 0.8%–5% of all cases of

brucellosis and represents the main cause of death due to brucellosis [2]. Mortality is usually caused by cardiac failure especially in patients with late diagnosis [3].

Brucella prosthetic valve endocarditis (PVE) is extremely rare, as it remains a diagnostic and therapeutic challenge, due to the lack of controlled trials and treatment approach regarding the ideal treatment duration, combination of antibiotics, indication and timing of surgery. The purpose of this

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study was to systematically review all published cases of *Brucella* PVE in the literature and describe the epidemiology, microbiology, clinical characteristics, treatment and outcomes of these infections.

2. Materials and methods

2.1. Data search

We reviewed all reported cases of *Brucella* PVE by searching PubMed, Google, Google Scholar and Scopus publications from January 1974 to the present. The used MeSH terms were: (Prosthetic valve OR valve prosthesis OR valve replacement OR bioprosthesis OR mechanical valve) and (brucella endocarditis or brucellosis and endocarditis). To find the old publications we used MeSH "Starr's valve and brucella endocarditis".

2.2. Study selection

We included the studies reporting data on patients' clinical characteristics, microbiology, treatment and outcome. We included all the studies published in different languages. The majority of the articles were in the English language ($n = 33$), three articles were in French, two articles were in Spanish and two articles were in Turkish. We excluded from the analysis the studies which were secondary research papers (e.g., reviews) and studies not in humans. *Brucella* endocarditis on the native valve and cardiac device were excluded. Given the rarity of the pathology, all articles on *Brucella* PVE were included in this literature review regardless of the type of article (letter to the editor, case report, cases included in case series) to gather as much information as possible. Data were extracted independently by the authors and any discrepancies were reviewed and discussed until consensus was reached, data were extracted from the reviewed text, tables, and figures. The clinical data including demographic characteristics, clinical features, laboratory data, echocardiographic findings, treatment, and clinical outcome of these patients were collected and analyzed.

2.3. Outcomes of interest

The primary outcomes were to record on the (a) epidemiology of patients with *Brucella* PVE and (b) patients' outcomes. Secondary outcomes were to record data on (a) the exact site of infection, (b) the patients' clinical characteristics, (c) their laboratory and echocardiographic features and (d) their

Abbreviations

PVE	Prosthetic valve endocarditis
IE	Infective endocarditis

treatment. The identification of risk factors for mortality was another endpoint of this study.

2.4. Data extraction and definitions

The extracted data included patient demographic data (age and gender); patient's relevant medical history (previous cardiac surgery or cardiac valve replacement, time after cardiac valve replacement); infection data and microbiology infection site, isolated strains, presence of complications, presence of embolic phenomena; treatment prescribed and outcomes (cure or death).

Diagnosis of infective endocarditis (IE) was confirmed by the investigators based on information provided by the authors and the modified Dukes' criteria if the diagnosis was definite (2 major or 1 major and at least 3 minor criteria, or 5 minor criteria) or if pathological data established a diagnosis of IE. The complications recorded included any organ dysfunction or clinical deterioration that was considered by the authors to be related to the IE.

2.5. Statistical analysis

All of the continuous variables are expressed as mean \pm standard deviation and the categorical variables as percentages. In univariate analysis, the Anova test or the Mann–Whitney test were used for the quantitative variables and the Chi-square test for the qualitative variables. A p-value < 0.05 was considered statistically significant. Due to the small number of patients, a multivariate analysis was not possible.

3. Results

3.1. Literature search

A total of 305 articles reporting *Brucella* endocarditis from PubMed, Google, Google Scholar and Scopus publications were screened. After reviewing the titles and abstracts, we identified a total of 41 articles of *Brucella* PVE. The full text of one article could not be found. We included a total of 40 articles reporting 51 cases (4–43) (Fig. 1). The first case of *Brucella* PVE has been published in 1974. Clinical,

biological, echocardiographic and therapeutic findings are summarized in Table 1.

3.2. Epidemiology

Most cases were from Turkey (21 patients, 42%), Spain (eight patients, 16%), and Iran (five patients, 10%) (Table 1). The mean age of patients was 42 ± 13 years [15–75 years], a male predominance was noted (34 males, sex ratio 2).

3.3. Microbiology

Brucella melitensis and *Brucella abortus* were the most frequently isolated species ($n = 29$, 56.8%). *B. melitensis* was isolated in 23 patients (45%), *B. abortus* in six patients (11.7%) and *B.suis* in one patient [35], None patient had *Brucella* PVE caused by *B. canis*. Consumption of unpasteurized dairy product, raw milk, fresh goat's cheese was reported in 22 cases (43%). Contact with infected animals and/or consumption of unpasteurized dairy milk has been reported in 26 patients (50.9%). Thirteen Patients (25.5%) were exposed by their profession or by their leisure activities: veterinarian in one patient [33], a stock- breeder in one patient [36],

hunter in two patients [8,35], shepherd in five patients [8,27,30,31] and farmer in four patients [18,38,39,42] (Table 1).

3.4. Underlying cardiopathy and comorbidities

Most common type of prosthesis valve was mechanical prosthesis ($n = 43$; 84.3%), eight (15.7%) patients had bioprosthetic valve [6–9,20,21,28,32], And ten patients (19.6%) had double valve prosthesis [5,18,19,23,29,31,32,36,39]. Prosthetic aortic valve involvement was reported in 27 patients (52.9%), prosthetic mitral valve involvement was reported in 18 patients (35.3%) and in two cases (3.9%) both the aortic and mitral prosthesis were affected [23,36]. No endocarditis in the tricuspid prosthesis valve was reported (Table 2).

The etiology of the valvulopathy for which the patient had a valvular replacement with valve prosthesis has been specified in 27 patients. It was rheumatic valvular heart disease in 15 of these patients (55.5%) [4,8,11,12,15,17,18,20,21,23,24,26,30,39] (Table 1). The average duration between implantation of the prosthesis and the episode of *Brucella* PVE was 8 ± 7 years (extremes: 4 months-

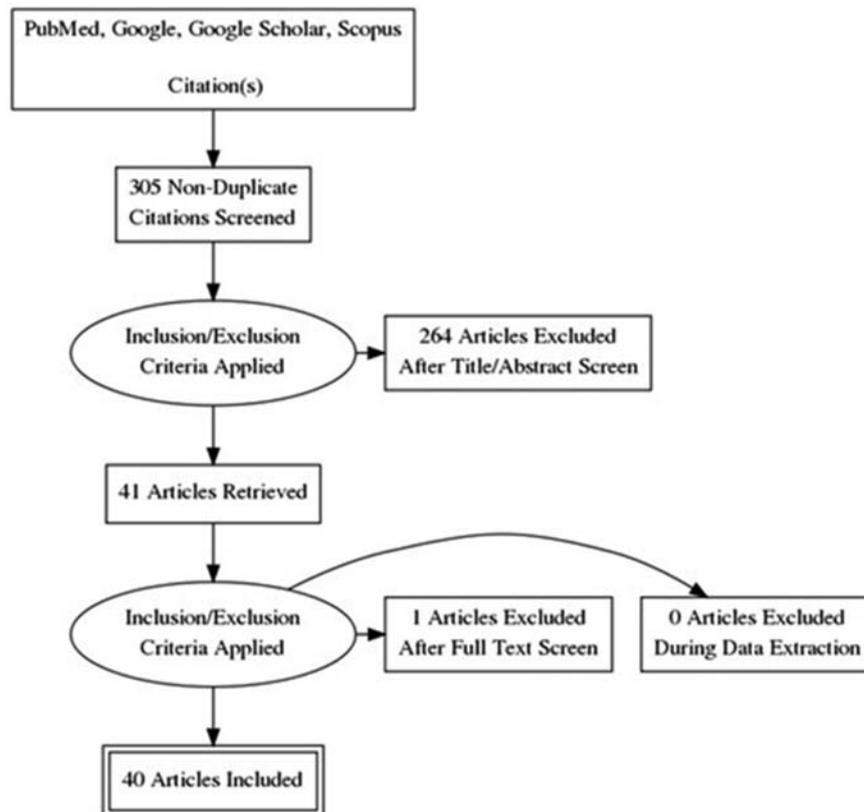


Fig. 1. Flow diagram of study inclusion.

Table 1. Clinical, biological, echocardiographic and therapeutic data of the reviewed cases of *Brucella* prosthetic valve endocarditis.

Authors year	Country	Age/sex	Risk factors: Consumption/ profession	Underlying cardiopathy	Symptoms and physical findings	Laboratory findings	Serological tests/blood culture	TTE/TEE findings	Complication Cardiac/extracardiac	Antibiotic combinations /total duration	Surgery/ surgical explorations Interval time diagnosis/surgery	Follow up
O'Meara J.B 1974 (4)	London/ Italian patient	38/ M	Yes	Mitral, mechanical Rheumatic 10 months	Fever, rigor, cough, dyspnea, abdominal pain	-	+/+ B.melitensis B. abortus	- Mitral prosthesis stenosis in cardiac catheterization	HF	Cephalexin, +Trimethoprim+ Sulphadiazine TS/12 months	Yes/V/- Ischemic stroke	-
Lezaun R 1980 (5)	Spain	48/ M	-	Double prosthesis aortic/mitral 5 years	Fever, dyspnea, petechiae Diastolic aortic murmur 1 month	-	+/+ B.melitensis Initial negative blood culture	- Severe paravalvular leak on aortic prosthesis in cardiac catheterization	HF	T+sulphadiazine =3 weeks	Yes/-negative Replacement of aortic and mitral prosthesis	1 year uneventful
Iglesias A 1981 (6)	Spain	28/F	-	Aortic Bioprosthesis Ventricular septal patch Congenital heart disease 3 years	Fever, phlebitis Signs of aortic regurgitation SMG 14months	-	+/+ B.melitensis	-	HF	Ts=8 weeks	Yes/A/D/ positive Interval time diagnosis-surgery: 5 days AV block corrected by pacemaker	6 months uneventful
Rubio Alvarez 1983 (7)	Spain	-	-	Bioprosthesis	Fever	-	-	-	-	-	No	Cured by antibiotherapy
Fernández Guerrero, 1987 Case 1 (8)	Spain	46/ M	No/-	Aortic, mechanical prosthesis Calcified AS 23 months	Fever, chills, dyspnea, general malaise Diastolic aortic murmur	Anemia ESR=84/113	+/+ B.melitensis	-	-HF -Pulmonary edema -atrio ventricular block	T+S then T/16weeks TS D/12 weeks after reoperation	Yes/D, A/positive Reoperation for disinsertion (no IE) Interval time diagnosis-surgery: 10days	4 years Uneventful
Fernández Guerrero, 1987 Case 2 (8)	Spain	60/ M	Yes/-	Aortic, mechanical prosthesis Rheumatic 2 years	Fever, chills back pain, Diastolic aortic murmur SMG/HMG 3 weeks	Anemia ESR=66/100	+/+ B.melitensis	-	HF sacroiliitis	S+T/3weeks T/6 weeks S+TS/15weeks D/2/4weeks	Yes/A D/positive Reoperation for disinsertion (no IE) Interval time diagnosis-surgery: few days	3 years uneventful
Fernández Guerrero, 1987 Case 3 (8)	Spain	62/ M	Yes/ Hunter	Aortic bioprosthesis IE on Bicuspid valve 10 months	Fever, chills SMG, HMG Diastolic murmur	Anemia ESR=28/56	+/-	-	HF	S+T/3weeks then D+TS/16weeks	Yes/A D/positive B.melitensis Interval time diagnosis-surgery: 8 days	2 years Uneventful
Fernández Guerrero, 1987 Case 4 (8)	Spain	33/ M	Yes/ Shepherd	Aortic, mechanical prosthesis <i>Brucella</i> endocarditis on native valve 4 months	Fever, chills, aches, sweats HMG, SMG Diastolic murmur 4 months	ESR=138/154	+/-	-	-	S+T/ then D+TS/16weeks D/40 Weeks	Yes/D/ positive B.melitensis Interval time diagnosis-surgery: few days	2 years Uneventful
Al-Kasab 1988 (9)	Saudi Arabia	25/F	-	Mitral bioprosthesis 3 years	Fever, dyspnea SMG, 2 nd heart sound, the new systolic murmur of MR	Anemia High ESR	+/- SAT titer positif for B. abortus	Moderately large V	-	T+TS=3weeks	Yes/-negative Post-operative ischemic stroke	Sudden death 1 year after the operation, of an unknown cause
D'Agrosa 1988 (10)	France	36/ M	-	Aortic, mechanical prosthesis IE (<i>brucella</i> highly probable) 14 years	Fever	-	+/+ B. abortus	A	AV Block Myocarditis HF	R+Quinolone	Yes/-/-	Uneventful
Flugelman MY 1990 (11)	Israel	25/ M	Yes	Aortic, mechanical prosthesis Rheumatic 1 year	Fever, weakness, anorexia Short systolic aortic murmur 2 months	ESR=25	+/+ B.melitensis SAT initially Normal Bone marrow culture+ns/+ B. Biovar I	Normal	None	T+S+R=4 weeks T+R=2 weeks	No	Apyrexia Decrease SAT Negatation blood culture
Kamoun S 1991 (12)	Tunisia	22/ M	-	Aortic, mechanical prosthesis Rheumatic 5years	Fever	-	-	-	HF	R+T Then R+Ofloxacin	Yes/A, D/positive	1 year Uneventful
A Antela 1992 (13)	Espagne	15	-	Mitral valve prosthesis mechanical	Fever 2 months	-	-	Valvular failure	Ischemic stroke	Antibiotherapy	Yes Medical treatment Not sufficient	Not sufficient
A M saadeh 1996 (14)	Jordan	-	-	Aortic mechanical prosthesis	Relapse after 6 months of recovery from brucellosis end occult splenic abscess	-	-	-	-	Prolonged ATB	Yes	Recovery

Table 1. (Continued).

Arslan H 1998 (15)	Turkey	27/ M	YES	Aortic, mechanical prosthesis Rheumatic 4 months	Fever, weight loss, cough, chest pain, dyspnea, HMG, headache, hemoptysis, arthralgia, Systolic thrill 1 month	Anemia ESR=90	+/+ B.melitensis	L/shunt aorta- left ventricular	HF	S+R+TS=3 months	Yes	3 months Uneventful
Uddin 1998saa (16)	Turkey				Fever Dyspnea III-IV		+/+			R+D+G	Yes Prosthetic valve culture+	Uneventful
Uddin 1998 (16)	Turkey				Fever Dyspnea III-IV		+/-			R+D+G	Yes Prosthetic valve culture-	Uneventful
Cakalaga oglu C 1999 (17)	Turkey	39/F	Yes	Mitral, mechanical prosthesis Rheumatic 15 years	Fever, general malaise, arthralgia	-	+/ns Initial SAT normal	V/L	Brachial mycotic aneurysm	R+D+TS, Replacement of D by ciprofloxacin (side effects) 12 months	No	4 years Uneventful
Akinci E 2001 (18)	Turkey	42/ M	Yes	Double prosthesis Mechanical aortic/mitral Rheumatic 8 months	Fever, chills, night sweats, arthralgia, skin rash, weight loss, dyspnea SMG, HMG Mitral murmur petechia 2 months	ESR=45 Anemia pancytopeni a	+/+ B.abortus	Involved prosthesis: Mitral V/L Normal aortic prosthetic	Renal insufficiency related to renal failure	R+D+G Then R+D/3 Months	Yes/-/positive Initially refused Interval time diagnosis- surgery: 95 days	7 months Uneventful Normalization of SAT
Al Soub 2001 Case 1 (19)	Qatar	29/ M	Yes	Double prosthesis Mechanical aortic/mitral	Fever, cough, sweating, anorexia Hemiparesis 9 months	Anemia ESR=33	+/+ B.melitensis	Involved prosthesis: Aortic V/L/A	Ischemic stroke	R+D+TS/ 20weeks	Yes/A/ Positive Interval time diagnosis- surgery: 4days	10 months Uneventful
Al Soub H 2001 Case 2 (19)	Qatar	39/ M	Yes	Aortic, mechanical prosthesis	Fever, sweat, anorexia Cough 3 Weeks	-	-/ + Brucella species	V		D+S Then D+R Then D+R+TS/13 WEEKS	Yes/-/negative Interval time diagnosis- surgery: 10days	1 year Uneventful
Al Soub H 2001 Case 3 (19)	Qatar	35/ M	Yes	Mitral, mechanical prosthesis	Fever, cough, sweating 3 months	-	+/-	V		R+D+TS Then R+D/10 Weeks	Yes/-/negative Interval time diagnosis- surgery: 11 Weeks	10 months Uneventful
Keleş C 2001 (20)	Turkey	42/F	Yes	Mitral bioprosthesis Rheumatic 6 years	Fever, weight loss Sweating, dyspnea 2 months	High ESR Normal WBC	+/+ B.melitensis	V: large Left atrium thrombus		R+D+S/ Then R+D/ 6 months and 6 weeks	Yes/V/ negative	At 6 months decreased serology titers
Karahoca gli M 2005 (21)	Turkey	58/ M		Aortic Mechanical prosthesis	Fever Fatigue 15 days	-	-/+ B.melitensis/ Negative initial SAT, Coinfection S. aureus	V (native mitral valve)	Acute myocardial infraction, pulmonary edema	Antibiotherapy against S. aureus Died before antibiotherapy against Brucella	No Died	
Kalayciog lu S 2005 (22)	Turkey	40/F		Rheumatic Mechanical prosthesis Mitral, Then Bioprosthesis mitral struck)	Fever, cough, Weakness, dyspnea		-/ PCR positive	V:7/4 mm	Sacroiliitis, ischemic stroke	D+R/ 3 months	No	3 years Uneventful
Al Dhahouk S 2006 (23)	German y Turkish patient	55 F	Yes	Aortic/Mitral prosthesis Rheumatic 18 years/2 years	Fever, sweats, fatigue, chest pain 4 weeks	Anemia CRP:114 ESR:70	+/+ B.melitensis	Involved prosthesis: aortic, mitral V 18-11mm A L	HF Pulmonary Edema	R+D/6 months (taken only two months) R+D+G=3 months R+Ampicillin/ 8weeks G/4 Weeks	Yes/-/ Initially refused	2 years Uneventful
Sayar N 2006 (24)	Turkey	58/F	Yes	Mitral, Mechanical prosthesis Rheumatic 28 years	Fever, fatigue, dyspnea, HMG, generalized pain Systolic murmur 2 months	CRP:143 ESR:47	+/-	2V:12/6 mm 9/5 mm Normal TTE	Torsade de Pointes, Ventricular fibrillation	D+R+TS/12 months	Yes/-/negative	12 months Uneventful
Tasbakan MI 2006 (25)	Turkey	50/F	-	Aortic, Mechanical prosthesis AS/ascending aorta dilation 4 years	Fever, chills, dyspnea, chest pain sweating, weight loss, arthralgia, diastolic murmur 2 months	Anemia ESR:56	+/+ B.melitensis	Valvular regurgitation	HF	D+R/3 months	Yes/-/positive Interval time diagnosis- surgery: 5days	24 months Normalization SAT
Murdaca G 2007 (26)	Italy	49/F	Yes Farmer	Mitral, mechanical prosthesis Rheumatic 10 years	Fever 3 weeks	Leukopenia ESR :70 CRP :180	-/+ Brucella Spp	V (TEE)		R+D+G/6 weeks	No	Negativation blood culture Disappearance of vegetation
Longo 2008 (27)	Tunisia	55/ M	Yes Shepherd Consumpti on of raw milk	Mitral Starr prosthesis 16 years ago	Fever Night sweating Fatigue 5 days	ESR=60 leucopenia	+/-	V(TTE, TEE) 6 mm	Glomerulo- nephritis	R+D+ofloxacin= 6 months	Yes After 3 months of antibiotic therapy	Serologic test became negative within 3 months 6 months: uneventful

Table 1. (Continued).

Botta L 2009 (28)	Bologna Turkish patient	68/ M	-	Aortic Bioprostheses AS 7 months	Progressive Fever Dyspnea Chills Sweats Weight loss Fatigue	-	ns/+ B.melitensis <i>Klebsiella</i> in only one	TTE/TEE Initially normal Aortic valve Severe aortic regurgitation on bioprosthesis Mitral, regurgitation without V	HF	D+R/ 8 weeks -After surgery Cefuroxim+G+D/ 2 weeks D+G/4 weeks D+R/3 Months	Yes/V/ positive PCR of vegetation Interval time diagnosis-surgery: 8 weeks	6 months Uneventful
Gunes Y 2009 (29)	Tukey	53/ M	-	Double prosthesis Mechanical Mitral/Aortic 6 years	Fever	ESR :60 CRP :20	+/+ B.melitensis	Involved prosthesis unknown Normal TTE TEE: refused		T+R+Ceftriaxone/ 36 Days Further treatment was refused	Surgery refused	DIED After 1 month
KARAOĞ LAN 2009 Case 1 (30)	Turkey	42 F	Consumption on raw milk	Mitral prosthetic valve Mechanical Rheumatic fever	headache, dyspnea and fever 2 weeks systolic murmur and	WBC :11000 /mm3 ESR=80	+/+ B.melitensis	vegetation on prosthetic mitral valve 8x9 mm TEE	Stroke Motor deficit	R+D+ Amikacin Then R+D+TS=12 mois	Proposed twice Refused	Vegetation disappeared and Brucella titers was decreased to <1/160 at 12 months
KARAOĞ LAN 2009 Case 2 (30)	Turkey	27/ M	sheep herder	Prosthetic aortic valve replacement 1 year Aortic stenosis Mechanical prosthesis	fever, dyspnea 1 month Murmur from aortic prosthesis		+/+ B.melitensis	Vegetation on aortic prosthesis 14/6 mm TEE		R+D+Ceftriaxon =1 month Then R+D=6 months	No	Vegetation disappeared SAT decreased to <1/160 at 6 months 12 months: uneventful
KARAOĞ LAN 2009 Case 3 (30)	Turkey	56/ M	Unpasteurized milk	Mechanical aortic valve replacement (Rheumatic) Fever coronary artery bypass grafting for coronary artery disease 7 years	Fever 2 weeks	Wbc :9000 ESR : 184	+/+ B.melitensis	Periannular abscess		R+D=6 months	No	Periannular abscess was disappeared and blood cultures were negative after 6 months follow up 12 months: uneventful
Keshtkar-Jahromi M 2010 Case 1 (31)	Iran	34/ M	Yes Shepherd	Double prosthesis Mechanical Mitral/Aortic	Fever, chills SMG 180 days	High ESR	+/-	Involved prosthesis: aortic A / L		R+D+ciprofloxacin/3 months	Yes/-/-	18 years Uneventful
Keshtkar-Jahromi M 2010 Case 2 (31)	Iran	61/ M	Yes Shepherd	Double prosthesis Mitral/tricuspid	Fever Chills 2 months HMG	Leucocytosis	+/-	Involved prosthesis: Mitral V 8/10 mm	Shock	Died before antibiotherapy	No	
Keshtkar-Jahromi M 2010 Case 3 (31)	Iran	16/F		Aortic Mechanical Prosthesis	Fever, arthralgia Erythema nodosum, purpura 30 days	Anemia	+/-	A V 8/5 mm Aortic aneurysm		D+R+TS+S/6 Months	Yes/-/-	<1 year
Sasmazel A 2010 Case 1 (32)	Turkey	42/F	-	Mitral bioprosthesis	Fever	-	-	V Mitral Degeneration in bioprosthesis		D+R+S/6 weeks Then D+R/6 months	Yes/-/- Surgery after 6 weeks	Died 10 years after surgery (Ischemic stroke) Well
Sasmazel A 2010 Case2 (32)	Turkey	45/ M	-	Double prosthesis Mechanical Mitral/Aortic	Fever	-	-	Involved prosthesis: Mitral V		R+T+TS/ 8 weeks R+T/ 10 months	Refused surgery	62 months Uneventful
Amirghofrane AA 2011 (33)	Iran	39/ M	-/ Veterinarian	Bentall Aortic Mechanical prosthesis	Fever, chills, hip pain, dyspnea 2 months	-	+/+ Brucella	Massive aortic root infected pseudoaneurysm, normal prosthetic valve leaflets	Right coronary involved In the infective process	R+Ciprofloxacin +T+G/1 months. R+Ciprofloxacin +T+/10 months.	Yes/D/- Bentall +CABG right coronary artery	1.5 years Uneventful
KEÇİK BOŞNAK 2011 (34)	Turkey	75/ M		Mechanical aortic Valve prosthesis Aortic insufficiency 4 months	Fever Chills Night sweating		+/+ B.melitensis	vegetation	A gastrointestinal side effect of Tetracycline	R+D+TS Then R+D+Ceftriaxon =2 months R+TS=4 months	No	Normalization of biological tests and disappearance of vegetation 1 year: uneventful
Carrington M 2012 (35)	USA	46/ M	-/Feral Swine hunter	Aortic Mechanical prosthesis Four separate aortic graft Marfan's syndrome 15 months	Fever, fatigue, malaise, abdominal pain, lower back pain, dyspnea SMG 15 months	pancytopenia	ns/+ B suis biotype I PCR positive		Shock Multiple Splenic infarct	Pancytopenia Multiple splenic infarct Myocarditis	Died before surgery	
Mehanic S 2012 (36)	Bosnia	46/ M	-/Stock breeder	Double Mechanical prosthesis Mitral/Aortic 9 years	Subfebrile, sweats, dyspnea, HMG, chest pain	Laboratory criteria for glomerulonephritis	ns/+ B.melitensis Coinfection with <i>Coxiella burnetii</i>	BOTH PROSTHESIS VALVE INVOLVED	Severe HF glomerulonephritis	Quadruple antimicrobial therapy	No Because cardiac instability	DIED In the fourth month

Table 1. (Continued).

					> 1 year HMG, splinter hemorrhages. Systolic/diastol ic murmur			Multiple V:7- 10mm Atrial thrombus				
Oguzhan N 2012 (37)	Turkey	50/M	-	Mitral Mechanical prosthesis 7 years	Fever, fatigue, anorexia, joint, back pain sweats, cough, weight loss, HMG, SMG 3 months	Anemia ESR:41 CRP:43 Creat: 353,6μmol/l	+/ns Hepatitis B	V15/2,5 mm Normal TTE	glomerulonephritis	D+R+Ceftriaxone/3weeks D+R/6 weeks	NO	No vegetation at 42 day
Raju T 2012 (38)	India	22/M	-/Farmer	Mitral Mechanical prosthesis Congenital mitral regurgitation 3 years	Fever Severe breathlessness 3 months	-	ns/+ <i>B.melitensis</i> <i>B.abortus</i>	Elevated gradient through mitral prosthesis	-	R+D+G/-	No DIED. Develop HF multorgan dysfunction and developed shock	
Lee SA 2014 (39)	Korea	42/M	-/Stock farmer	Mitral Mechanical prosthesis 22 years Tricuspid Mechanical Rheumatic 18 years	Fever Dizziness Sweats Dyspnea 2 months	Severe anemia CRP:57.6 mg/l Leucopenia: WBC: 2600	+/ <i>B abortus</i>	Involved prosthesis: mitral V (TEE) 3-8 mm	-	D+R+S Then D+R+G Then D/1 years	NO Refused (history of three opened cardiac surgery) Disappearance of V	After 3 weeks: negativation blood culture 5 years Uneventful
Aktürk S 2015 (40)	Turkey	36/M	-	Aortic Mechanical prosthesis 4 years	Fever, muscle pain, back, chest pain New onset of symptoms	-	ns/+ <i>B.melitensis</i>	V	Acute myocardial infarction related to occlusion of circumflex coronary artery	-	-	-
Dehghan Manshadi SA 2016 (41)	Iran	35/M	-	Bentall procedure Aortic Mechanical prosthesis IE complicated with splenic abscess 4 years	Fever, loss of weight, loss of consciousness, low back pain 4 months	-	+/ns Hepatitis B	V:36/11mm Aortic regurgitation	Spondylodiscitis meningitis	D+R+Ceftriaxone+G Then R+D+TS	No DIED Hepatorenal and cardiac insufficiency	
Fonseca JP 2018 (42)	Portugal	60/F	Yes/Farmer	Aortic Mechanical prosthesis AS 4 years	Fever, loss of weight, low back pain, asthenia Aortic systolic murmur 3 months	Mild leukopenia CRP:46 mg/l	+/ <i>B.melitensis</i>	Normal TTE TEE: V	Spondylodiscitis	R+D+G/3weeks R+D/9 months (negativation SAT)	No Judged non-necessary	Shrinkage of vegetation 2 years Uneventful
Hamieh 2020 (43)	Lebanon	37/M	Yes: Row milk intake	Aortic Mechanical prosthesis 20years	Fever, night sweating, generalized fatigue 3 months	Lactate : 87.7 mg/dl. Procalcitonin :0.95 ng/mL	+/- PCR -	Prosthetic dehiscence, severe paravalvular regurgitation, low ejection fraction (34%)	Septic and cardiogenic shock	R+D/3weeks then R+D+Ceftriaxone	Surgery planned but not performed due to hemodynamic instability Died 24H after admission	

+: Positif, -: Negatif, ns: not specified

A: Abscess, AR: Aortic regurgitation, AS: Aortic stenosis, AV: Atrioventricular, CRP: C reactive protein, D: Prosthetic valve disinsertion,(mg/l), ESR: Erythrocyte sedimentation rate mm/h, HF: Heart failure, HMG: Hepatomegaly, IE: infective endocarditis, L: Leak, MS: mitral stenosis, MI: mitral insufficiency, MS: Mitral stenosis, PCR: Polymerase chain reaction, SAT: Serum agglutinin test, SMG: Splenomegaly, V: Vegetation, WBC: White blood cells.

Antibiotics: R: Rifampicin, D: Doxycycline, S: Streptomycin, G: Gentamicin, T: Tetracyclin, TS: Sulfamethoxazole, and Trimethoprim.

28 years). Early *Brucella* PVE was noted in eight patients [4,8,11,15,18,21,28,34]. Only three patients had comorbidities, two patients had diabetes [21,28] and one patient had cardiac liver cirrhosis [39].

3.5. Clinical presentation

The commonest symptoms were fever, chills, night sweating, dyspnea, fatigue, weight loss, osteo-articular and muscular symptoms. The mean duration of the symptoms before diagnosis was 3 ± 3 months (with extremes ranging from one week to 15 months). This duration was between two months and one year in ten patients [8,19,31,37,38,41–43], less or equal to two months in 24 patients [5,8,9,11,13,17–20,22–28,30,31,33,39,40] and above one year in four patients [6,15,35,36]. It was not specified for the rest of the patients.

In 11 patients (21.5%), one or more hospitalizations because of fever preceded by a few weeks the diagnosis of *Brucella* PVE [5,6,19,21,23,28,35,36]. In three patients among them, the diagnosis of brucellosis was determined but patients had failed standard treatment for brucellosis [23,28,43]. In patients reported by Al Dhahouk et al. [23], Mehanic et al. [36], Carrington et al. [35], and Hamieh et al. [43], echocardiography was not performed at the time of diagnosis of brucellosis. We can't precise whether they had endocarditis from the beginning or endocarditis developed later during the course of the disease. In the patient reported by Botta et al. [28], transthoracic and transesophageal echocardiography were normal.

A history of IE was found in six patients [8,10,14,36,41] among them three patients [13,15,19] had a history of *Brucella* endocarditis, reinfection has occurred one year, 14 years and 6 months,

respectively. Relapse of brucellosis after an appropriate treatment was recorded in five patients [8,10,14,33,42]. Mean duration of symptoms before the diagnosis of PVE was also prolonged in patients with a history of brucellosis (brucellosis with failure of treatment, relapse, history of brucella endocarditis) [8,10,14,23,28,33,42] ranging between 2 and 4 months. Heart failure was noted in 16 patients (31.3%).

3.6. Biological findings

Diagnosis of brucellosis was made by serology and/or culture in all except one patient [21]. Blood culture was positive in 31 patients (60.7%). It was negative in 20 patients (39.3%), in these patients the diagnosis of brucellosis was done by the serologic tests. Both positive blood culture and serologic tests were observed in only 23 patients (4%). Two patients with positive blood culture were seronegative [19,26]. Results of serologic tests were not mentioned in six patients [12,28,35,36,38,40]. PCR test was performed in only three patients [22,35,43]. It was positive in two patients among them [22,35]. It allowed the diagnosis of brucellosis in one patient with negative blood culture and negative serologic tests [21]. Bone marrow culture was performed in one patient, it was positive [11]. In this patient, both blood culture and serologic tests were positive.

3.7. Echocardiographic findings

Echocardiographic data were available in 32 patients (62.7%) (not performed in eight patients, this technique of imaging was not developed at the time [2–4,4–8]). Echocardiographic data of the rest of patients were not available. It was abnormal in 30 of them (93.7%). Twenty-seven (84.3%) patients had vegetation, in eight patients among them a large vegetation (size equal or above 10 mm) was noted (29.6%) [9,20,23,24,30,31,36,41].

In three patients vegetations was detected in transesophageal Echocardiogram, it was not shown in transthoracic echocardiogram [24,37,42]. Six patients had abscess [1,10,23,30,31] and 11 patients had paravalvular leak and regurgitation [15,17–19,23,25,28,31,32,41,43].

An Aorta-left ventricle fistula was seen in the patient reported by Arslan et al. [15], a massive aortic root infected pseudoaneurysm was reported by Amirghofrane et al. [33] and an aortic aneurysm was reported by Keshtkar et al. [31]. In old reports, cardiac catheterization has shown a mitral prosthetic valve obstruction in one patient [4] and a

severe leak in the aortic prosthetic valve in another patient [5].

3.8. Treatment

Mean duration of treatment was 6 ± 3 months [1–14 months]. There was no standard antibiotic regimen used. Most used antibiotics are Rifampicin, Doxycycline (or Tetracycline) and Aminoglycoside (Streptomycin or Gentamycin), or Co-trimoxazole. Co-trimoxazole (Trimethoprim-Sulfamethoxazole) was prescribed in 16 patients (31.3%). Quinolones (ciprofloxacin or ofloxacin) were used in six patients (11.7%) and cephalosporin antibiotics were used in seven patients (13.7%). Sulfadiazine was prescribed in one patient (2%) [5] (Table 1). The effect of antibiotics on mortality cannot be assessed owing to the small number of patients.

3.9. Comparison of medical treatment alone versus combined surgical and medical treatment

We identified 29 patients (56.8%) who had combination of medical and surgical treatment (group 1) [4–6,8–10,12–16,18–20,23–25,27,28,31–33] and 18 patients (35.2%) who had medical treatment alone (group 2) [7,11,17,21,26,29,30,32,34,36–39,41–43]. Three patients (5.8%) have died before treatment [22,31,35] (Table 3).

No difference was noted between the two groups concerning age and sex, with p-value at 0.18 and 0.77, respectively. The mean duration of symptoms before diagnosis was 3 ± 3 months in group 1 and 4 ± 3 months in group 2 ($p = 0.51$). The incidence of heart failure was similar in the two groups ($p = 0.22$) (Table 2). No difference was noted between the two groups concerning positivity of blood culture ($p = 0.49$). The mean duration of treatment in group 1 was 6 ± 3 months [3 weeks-13 months] and in group 2 was 7 ± 5 months [6 weeks-12 months] ($p = 0.52$). In patients who underwent surgery (group 1): The median duration of antibiotics until surgery was 10 days [5–66 days].

The most frequent indications for surgery were: Failure of medical treatment with uncontrolled infection and enlarging or persistence of vegetation despite antibiotics [9,13,18,24,27,33], valvular regurgitation, and congestive heart failure in 12 patients [4–6,8,10,12,15,23,25,28], preventing embolic complications [20], relapse after recovery by antibiotics alone [14] and severe hemodynamic instability which developed during antibiotic therapy [16]. Intracardiac complications with abscess in five patients [10,19,23,31] and an aortic root infective pseudoaneurysm in one case [33] were indication

Table 2. Clinical presentation and complications of the reviewed cases.

	Number	Percentage (%)	References
Clinical presentation			
Fever	51	100	[4–43]
Dyspnea	19	37.2	[4,5,8*,9,15,16**,20,21,38,24,25,28,30***,33,35,36,39] *Case 1,**Case 1,2, ***Case 1,2
Night sweating	15	29	[8,18–20,23,25,27,28,34,36,37,39,43]
Fatigue, asthenia, weakness	14	27	[11,18,21–25,27,28,35–37,42,43]
Chills	12	23.5	[8*,18,25,28,31**,33,34,36] *Case 1,2,3; **Case 1,2,3
Osteoarticular symptoms	10	19.6	[8*,15,17,18,24,25,33,35,27,40,31**] *Case 4, **Case 3
Splenomegaly	9	17.6	[6,8*,9,18,31,35,37] *Case 2,3,4
Hepatomegaly	9	17.6	[8*,15,18,24,31**,36,37] *Case 2,3,4; **Case 2
Weight loss	7	13.7	[15,18,20,25,28,37,42]
Associated sites			
Sacroiliitis	2	3.9	[8*,21] *Case 2
Spondylodiscitis	2	3.9	[41,42]
Underlying cardiopathy			
DVP: Mitral and aortic prosthetic	8	15.6	[5,18,19*,23,29,31**,32***,36] *Case 1,**Case 1,***Case 2
DVP: Mitral and tricuspid prosthetic	2	3.9	[31] Case 2, [39]
Aortic prosthesis	21	41	[6,8*,10–12,14,15,19**,22,25,28,30***,31****,40,42,34] *Case 1,2,3,4; **Case 2; ***Case 2,3,****Case 3,43
Mitral prosthesis	14	27.4	[4,9,13,17,19*–21,24,26,27,30**,32***,37,38] *Case 3, **Case 1, ***Case 1
Bentall intervention	2	3.9	[33,41]
Aortic graft and mechanical aortic prosthesis	1	1.9	[35]
Complications			
Heart failure	16	31.3	[4–6,8*,10,12,15,22,23,25,28,36,38,41,43] *Case 1,2,3
Septic shock	1	1.9	[43]
Myocarditis	2	3.9	[10,35]
Myocardial infarction	2	3.9	[22,40]
Rhythm disturbance	1	1.9	[24]
Atrioventricular block	1	1.9	[10]
Artery mycotic aneurysm	1	1.9	[17]
Ischemic stroke	4	7.8	[13,19,21,30]
Glomerulonephritis	3	5.8	[27,36,37]
Renal failure	1	1.9	[18]
Meningitis	1	1.9	[41]
Multiple splenic infarct	2	3.9	[14,35]

DVP: Double valve prosthesis.

for surgery. In two patients, surgery was initially refused and performed later when antibiotic therapy alone was inefficient [18,23].

The echocardiographic findings were confirmed during surgery in all the patients except the patient reported by Amirghofrane et al. [33], prosthetic valve disinsertion was noted intraoperatively but not shown in echocardiography. In five patients in whom echocardiography was not performed (the technique was not developed at the time), surgical examination revealed abscesses in five patients [6,8,12] and dehiscence of prosthetic valve in six patients [6,8,12].

Culture of vegetation, excised tissues, or prosthesis valve was positive in ten patients [6,8,16,18,19,25,28]. All

of them had positive blood culture except two patients [8], among whom the diagnosis of brucellosis was determined by serologic tests. In three patients [18,23,28], culture of the prosthesis was positive despite appropriate and prolonged antibiotics, with treatment duration respectively at 95 days, 2 months, and 8 weeks.

All patients who underwent surgery were cured by combination surgery and antimicrobial therapy (Fig. 2). Few postoperative complications have been reported, including a regressive ischemic stroke in two patients [4], atrioventricular block treated by a pacemaker in one patient [6], and reoperation in two patients for desinsertion of the valve prosthesis without signs of endocarditis [8].

Seventeen patients had antibiotic therapy alone (group 2), among them 13 patients have been cured [7,11,17,21,26,30,32,34,37,39,42] and four patients have deceased [29,36,38,41] (Fig. 2). In patients cured by antibiotic therapy alone, surgery was planned but refused by the patients in three cases [30,32,39]. In the other patients [7,11,17,21,26,30,34,37,42], surgery was not performed because there were no heart failure and prosthetic dysfunction with good evolution and disappearance of vegetation. In group 2, therapeutic choice (medical treatment alone) was consistent with current guidelines [48] in all these patients except in the patient reported by karaođlan et al. [30] in which cardiac abscess was treated by antibiotics alone, and the patient reported by Mehanic et al. who had heart failure [36].

The average follow-up was 1 year [0,5–18 years], no significant difference was noted between the two groups ($p = 0.56$). Neither relapses nor late death related to *Brucella* PVE was noted in the two groups. Sudden death of unknown cause has occurred in one patient one year after surgery [9].

3.10. Early mortality

Early mortality was noted in 16% of the cases (8/50 patients). There was no information about treatment in one patient. Five patients were treated with antibiotics alone, and three patients with PVE died before the diagnosis of *brucella* PVE [22,31,35]. No deaths were noted in patients treated by combined medical and surgical treatment, but mortality was noted in 27.7% of the cases treated by antibiotics alone (5/18). Table 4 summarize clinical and para-clinical data in deceased patients compared to cured patients.

4. Discussion

Human Brucellosis is the most frequently encountered world-wide zoonotic disease, it affects both adult and child and remains a major human health problem in many developing regions, especially in the Mediterranean basin, North and East Africa, the Middle East, the Arabian Peninsula, the Indian subcontinent and parts of South America and Central Asia [44,45]. According to the World Health Organization, 500,000 new *Brucella* cases are reported each year with a prevalence of more than 10/100,000 population is noted in endemic countries [46].

4.1. Clinical presentation and risk factors of brucellosis

As noted in this review, the disease affects mostly the young population. The infection is usually associated with contact with infected animals or through the consumption of unpasteurized dairy milk [44]. A careful assessment of epidemiological risk factors is crucial for the diagnosis of brucellosis. In reported cases, these risk factors were not sought in nearly half of the patients. Clinicians should obtain information about patient activities including travel, food consumption, occupation, and outdoor recreation. *Brucella* species should be considered in the differential diagnosis of PVE in patients leaving or returning from a region of endemicity. This review emphasizes the importance of performing a detailed patient interview, as it can provide useful information regarding potential exposure to infectious agents.

Human brucellosis is a multisystemic disease with a large spectrum of symptoms [2]. In the cases

Table 3. Clinical, biological, echocardiographic data among patients treated with combined treatment (group 1) and patients treated by antibiotic therapy alone (group 2).

	Group 1 (n = 29)	Group 2 (n = 18)	P-value
Age (years)	40 ± 14	45 ± 13	0.18
Gender (male)	18	15	0.77
Duration of symptoms before diagnosis (months)	3 ± 3	4 ± 3	0.51
Heart failure	10	5	0.22
Double prosthesis	4	5	0.45
Mechanical prosthesis	19	17	0.09
Prosthetic disinsertion	15	2*	0.002
Cardiac abscess	10	1**	0.04
Negative blood culture	12	5	0.49
Follow up duration (years)	2 ± 4	4 ± 3	0.56
Mean duration of antibiotherapy (months)	6 ± 3	7 ± 5	0.52

Group 1: patients treated with medical and surgical treatment, group 2: patients treated with medical treatment alone. Bold value indicates the difference between the groups was significant ($p < 0.05$).

*Two patients with disinsertion of the prosthesis were not received surgery, in the patient reported by Cakalagaoglu C, medical treatment was chosen as the adequate treatment option, and in the second patient, surgery was planned but the patient is deceased before. ** *Brucella* prosthetic valve endocarditis complicated with periannular abscess treated with antibiotherapy alone.

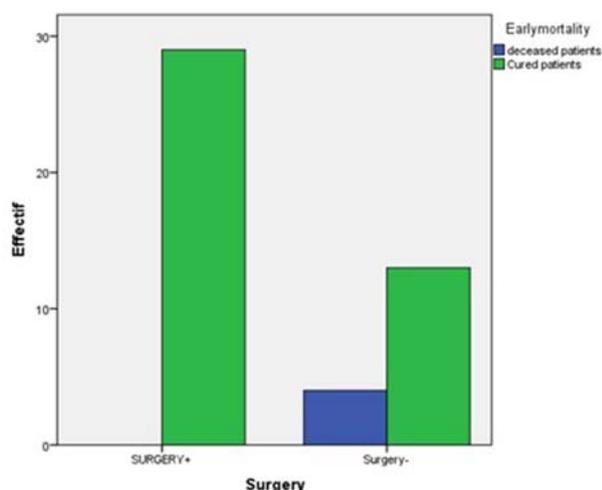


Fig. 2. Early mortality among treatment group and medical treatment alone group (Surgery + : Combined medical and surgical therapy, Surgery -: Medical treatment alone).

analyzed here, the spectrum of symptoms is closer to that of brucellosis than that of PVE. In patients with a prosthetic valve, brucellosis must be evoked when fever is associated with night sweating, muscle pain, arthralgia, back pain, and spondylodiscitis, especially in patients with risk factors. Relapse of brucellosis was noted in five patients. Relapsing bacteremia after appropriate treatment for acute brucellosis is an important clue for the diagnosis of brucella endocarditis in patients who have prosthetic valves [8,10,14,33,42].

In this current review, heart failure was frequent and represented a risk factor of mortality. It remains the most common cause of death due to IE and the most frequent reason for surgery in these patients [3,28].

4.2. Diagnosis work-up and challenges

Brucella PVE remains a diagnostic challenge. Meticulous history taking, clinical examinations,

and detailed laboratory tests such as serologic tests and blood culture, and echocardiography are required through the diagnosis process. In the reviewed cases, prolonged interval time between the onset of symptoms and diagnosis of *Brucella* PVE was noted. This interval time was prolonged even in patients with a known history of brucellosis. The delayed diagnosis can be explained by the difficulty in the culture of *Brucella* species and the lack of specificity of symptoms. Brucellosis is often misdiagnosed. By screening for *Brucella* antibodies of all sera from febrile patients, Purwar et al. reported almost two new cases per month of brucellosis, most of which are not suspected by clinicians [47]. According to some authors, Serious damage is likely to be caused not so much by the supposed poisonousness of the bacteria as by a late diagnosis due to the difficulty in the culture of this agent [48]. Special attention is then necessary for patients with prosthetic heart valves.

In cases reviewed here, a high rate of negative blood culture was noted (39.3%). *Brucella* endocarditis is often culture-negative endocarditis. In many series, it forms part of the pool of cases of pathogen-induced endocarditis with negative blood cultures. A negative culture could potentially lead to a delay in diagnosis and treatment [31]. Blood cultures, although highly specific, present a low sensitivity (15–70%) due to the low growth rate of *Brucella* spp., the necessity of proper culture medium, and their fastidiousness. In patients with PVE and negative blood culture, a high degree of suspicion of *brucella* PVE is needed especially in young male patients with a history of exposure to farm animals.

Due to the lack of sensitivity of blood cultures, serology is being used increasingly to allow an early diagnosis and is a major criterion in Duke's criteria [49]. However, serologic tests are not wholly specific, may be difficult to interpret in endemic areas, and maybe negative during the early stages of the

Table 4. Clinical and paraclinical data in deceased and cured patients.

	Deceased patients (n = 8)	Cured patients (n = 43)	P-value
Heart failure*	5	10	0.04
Age (Years)	45 ± 13	41 ± 14	0.50
Gender (male)	8	25	0.06
Negative blood culture	5	25	0.6
Large vegetation	3	4	0.04
Antibiotherapy alone/combined treatment**	8/0	10/29	0.006
Desinsertion of the valve prosthesis	0	16	0.01
Intracardiac abscess	0	11	0.26

OR: Odds ratio, CI: Confidence interval.

*Heart failure at admission, **Combined treatment: Surgery combined with medical treatment (antibiotherapy).

disease. They are considerably more reliable in the diagnosis of brucellosis when evaluated together with a consistent clinical presentation. In the majority of the cases reviewed here, the diagnosis was made initially by the serologic tests.

In this review, two seronegative patients with positive blood culture were reported. In literature about *Brucella* endocarditis, 6% of the patients with acute brucellosis present with an initial titer $\leq 1/160$, but it becomes at least four-fold higher on subsequent testing [50]. According to some authors, serologic tests are not suitable for the follow up of patients since titers can remain high for a prolonged period [51]. The high sensitivity and specificity of the PCR assays may provide a valuable tool for the diagnosis of brucellosis which is the case of the patient reported by Kalaycioglu et al. [22].

In cases reviewed here, echocardiography played a crucial role in the diagnosis of *Brucella* PVE and its complications. When available, echocardiography has been used as the first-line diagnostic approach and it allowed the diagnosis of endocarditis in the majority of cases. Some authors [52] recommended echocardiography in all patients with *Staphylococcus aureus* bacteremia because of the high frequency of endocarditis in such cases and because of the high morbidity and mortality of *S. aureus* endocarditis. In the same vein, can we suggest the systematic practice of echocardiography in all patients with cardiac valve prosthesis and brucellosis. This suggestion is supported by analyzing the echocardiographic findings in reviewed cases. *Brucella* PVE was misdiagnosed in some febrile patients or patients with a confirmed diagnosis of brucellosis because repeated echocardiography has not been done [19,23,33,35,36,42,43].

Brucella spp. can cause destruction and ulceration in tissues slowly, explaining the frequency of paravalvular leakage reported in 19 cases (37.2%) (revealed by echocardiography, cardiac catheterization, and surgical examination) and abscesses reported in 11 cases (21.5%) (revealed by echocardiography and surgical examination). These intracardiac complications reflect the severity of the disease. When compared with other bacterial pathogens, *Brucella* endocarditis is characterized by a greater tendency toward fibrosis, hyalinization, and calcification involving the cardiac valves. Therefore, due to its rapid and wide tissue destruction, higher mortality rates were observed during this disease [1,38,39,49] and has been noted in this review. Nearly the third of reviewed cases have large vegetation, which could be explained by the diagnostic delay and the prolonged evolution before the echocardiography is performed.

4.3. Treatment approach

Owing to the lack of large series, the optimal association, and duration of antibiotics is unknown. The intracellular location of the microorganism makes it inaccessible to the action of many antibiotics [53]. Ideally, the antimicrobial agent should be bactericidal to prevent relapse in brucellosis [54]. According to some authors, the addition of a third-generation cephalosporin (ceftriaxone), to the combination of a tetracycline group and rifampicin was more effective than aminoglycosides [55]. Quinolones such as ofloxacin and ciprofloxacin are the alternative drugs in combination therapy of brucellosis. They can be included due to their great tissue distribution and a great capacity to penetrate in vegetations in patients with IE and PVE [48].

Long-term treatment is necessary for *Brucella* infection since it is an intracellular and antibiotic-resistant infection [49,56]. By analyzing data of reviewed cases, it seems to be unanimous agreement on the need to prolong the *Brucella* PVE therapy, but there is no fixed duration in all patients. The mean duration of antibiotics varied from 1 month to 14 months. Prolonged therapy is necessary, before and after surgery, mostly in patients with prosthesis valve culture positive. In current guidelines, a duration of over 3–4 months was recommended in patients with *Brucella* endocarditis [49]. We believe that a longer duration of antibiotics may be necessary in cases of *Brucella* PVE.

Combined treatment associating surgery and medical treatment versus medical treatment alone was debated. Although recovery has been reported with antibiotics alone, surgery after medical treatment has been adopted as the most common therapeutic approach. In articles reviewed here [4–6,8–10,12–16,18–20,23–25,27,28,30–33,39] and in the literature about *Brucella* endocarditis (on the native valve and prosthetic valve) [22,56,57], authors suggest an early surgical approach with preoperative antibiotic therapy and immediate surgery after clinical stabilization due to the degree of tissue ulceration and destruction caused by *Brucella*. The high rate of recurrence and resistance of *Brucella* to medical treatment and development of large vegetations carrying a significant risk of embolization [25]. Other studies reported cases of *Brucella* endocarditis cured by antibiotics alone [7,11,17,21,26,30,32,34,37,39,42,58–60]. They stress the need for prognostic stratification of each case and support conservative treatment in low-risk cases without cardiac failure and with a short disease interval medical treatment. According to

them, careful monitoring is necessary because recurrence risk is high. All cases of *Brucella* endocarditis cured by medical therapy alone were reviewed by Mert et al. [58], who thought that the probable success of medical therapy was attributable to the absence of the compelling indications for surgery, such as heart failure, valve destruction, abscess formation or prosthetic valves dysfunction.

The results of this literature review support the opinion of the authors that believe that surgery is the most efficient approach for the treatment of *Brucella* PVE by showing a significant decrease in mortality in the group of patients treated with surgical treatment compared to the group of patients treated with antibiotics alone. Moreover, this superiority of surgical treatment was observed despite the lack of difference between the two groups in terms of clinical presentations. Given the slowly destructive character of *Brucella* *Spp.*, relapses, the multiple antibiotics needed to control this infection, her prolonged duration and the improved outcome with surgery, the question that arises is “Can we add *Brucella* species to the microorganisms listed in the guidelines related to the management of IE (Staphylococci or non-HACEK gram-negative bacteria and fungi) [49] to be considered as an indication for surgery?”. However, the number of patients reviewed here is limited which does not allow a recommendation.

4.4. Limitations

Although this review is the only and the largest one evaluating the diagnosis and therapeutic approach in *Brucella* PVE, it relies entirely on retrospectively published data, in some cases, crucial information is missing. Another important limitation is the small number of patients resulting in restricted statistical analysis. Therefore, the results of the survival analysis could not be extended by multivariate analysis. Moreover, because the review spanned many decades, during them the diagnosis, definition, surgical indication, and antibiotic treatment of endocarditis changed, this must be considered a limitation in interpreting the data.

5. Conclusion

This review points out the main reported characteristics of *Brucella* PVE, highlights the difficulties in its diagnosis. *Brucella* *spp.* should be considered as one of the etiologic agents of PVE in patients living or returning from endemic region, with a history of ingestion of unpasteurized dairy products and/or exposure to animals with prolonged and unexplained fever especially in patients with negative

blood culture and clinical signs suggestive of brucellosis that must be carefully researched. Earlier diagnosis and treatment lead to decreasing morbidity and mortality related to this infection.

Optimal treatment of *Brucella* PVE is a subject of great controversy. We suggest that successful management of *Brucella* PVE requires a combination of medical and early surgical therapy to achieve the sterilization of infected cardiac tissue and to replace the infected prosthesis valve, but given the limited number of patients, a formal therapeutic approach cannot be validated.

Summary section

Brucella prosthetic valve endocarditis affects mostly the young population with risk factors.

Brucella prosthetic valve endocarditis is usually culture-negative endocarditis. High rate of negative blood culture was reported, in almost 40% of the cases.

Echocardiography has a crucial role in the diagnosis of *Brucella* prosthetic valve endocarditis and its complications.

Although recovery was reported with antibiotics alone, combined medical and surgical therapy is the most efficient therapeutic approach as a significant decrease in mortality was reported.

Author contribution

Karima Taamallah: Conception and design of Study; Literature review; Acquisition of data; Analysis and interpretation of data; Research investigation and analysis; Data collection; Drafting of manuscript; Data preparation and presentation; Supervision of the research. **Fatma Hammami:** Conception and design of Study; Literature review; Acquisition of data; Analysis and interpretation of data; Research investigation and analysis; Data collection; Drafting of manuscript; Revising and editing the manuscript critically for important intellectual contents; Data preparation and presentation; Supervision of the research; Research coordination and management. **Hédi Gharsallah:** Acquisition of data; Research investigation and analysis; Data collection; Drafting of manuscript; Revising and editing the manuscript critically for important intellectual contents. **Makram Koubaa:** Conception and design of Study; Literature review; Acquisition of data; Analysis and interpretation of data; Research investigation and analysis; Drafting of manuscript; Revising and editing the manuscript critically for important intellectual contents; Data preparation and presentation; Supervision of the research; Research coordination and management.

Mounir Ben Jemaa: Conception and design of Study; Data collection; Revising and editing the manuscript critically for important intellectual contents; Supervision of the research; Research coordination and management. **Wafa Fehri:** Conception and design of Study; Revising and editing the manuscript critically for important intellectual contents; Supervision of the research; Research coordination and management

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Conflict of interest

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