original article

Clinical manifestations and treatment outcomes of human brucellosis at a tertiary care center in Saudi Arabia

Jameela Edathodu,[a] Maha Alamri,[a] Khadijah Ahmed Alshangiti,[a] Noura S. Alfagyh,[a] Ahmed S. Alnaghmush,[a] Faisal Albaiz,[a] Bader Alothman,[a] Hala Khalil,[b] Zenusha Edathodu,[c] Abdulrahman A. Alrajhi[a]

From the [a]Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [b]Department of Biostatistics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia; [c]Research Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Correspondence: Dr. Jameela Edathodu · MBC 46 Department of Medicine, King Faisal Specialist Hospital and Research Centre, PO Box 3354 Riyadh 11211, Saudi Arabia · jedathodu@kfshrc.edu.sa · ORCID: https://orcid.org/0000-0002-8688-7946

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BACKGROUND: Brucellosis, which has profound public health and economic consequences, is endemic to Saudi Arabia. *Brucella* is transmitted to humans by direct contact with infected animals or by consumption of unpasteurized dairy products. Manifestations of brucellosis are protean and require a combination of drugs to prevent the emergence of resistance. The WHO recommends the use of doxycycline with rifampicin or an aminoglycoside for brucellosis, but experts in Saudi Arabia prefer to avoid the use of rifampicin and aminoglycosides to lessen the possibility of emergence of drug-resistant tuberculosis.

OBJECTIVES: Compare rifampicin and doxycycline in the treatment of human brucellosis versus various combinations of doxycycline, with either trimethoprim-sulfamethoxazole (co-trimoxazole), quinolones or aminoglycosides, and describe the clinical manifestations of brucellosis.

DESIGN: Retrospective medical record review.

SETTING: Single tertiary care center.

PATIENTS AND METHODS: Diagnosis of brucellosis was based on positive serology by standard agglutination test (SAT), or isolation by culture of *Brucella* species from blood, body fluid or tissue.

MAIN OUTCOME MEASURES: Cure rate with the use of doxycycline in combination with either co-trimoxazole, quinolone or aminoglycosides in comparison to doxycycline/rifampicin and the clinical features of brucellosis.

SAMPLE SIZE: 123.

RESULTS: In 118 (96%) patients, the median IgG/IgM antibody titers at diagnosis and at 6 and 12 months were 1:1280/1:1280, 1:640/1:640, and 1:320/1:160, respectively. There were no differences in outcome between treatment regimens, as evidenced by a significant decrease in SAT titers and symptom resolution within six months. Five (4%) patients relapsed from non-adherence to treatment, but responded well to a second course of treatment. Blood cultures were positive in 50 patients (41%) patients. Fever, arthralgia and back pain were the most common symptoms. Good serological and clinical responses were achieved in 96% of patients. Relapse in 4% (n=5) was due to self-reported non-adherence.

LIMITATIONS: Retrospective, relatively small sample size.

CONCLUSIONS: Doxycycline with co-trimoxazole is as efficacious as doxycycline/rifampicin in non-focal brucellosis and is preferred in countries with a high prevalence of tuberculosis.

CONFLICT OF INTEREST: None.

Brucellosis is a zoonotic bacterial infection caused by several *Brucella* species, commonly *B melitensis*.[1] It is considered the most common zoonotic disease worldwide with the highest prevalence in the Mediterranean region, central Asia, India, parts of Mexico, and Central and South America.[2] Saudi Arabia is one of the endemic countries in which brucellosis has profound public health and economic consequences.[3,4] The total number of cases reported by the national registry of the Ministry of Health of Saudi Arabia was 37 477 from 2004 to 2012, with a decrease in more recent years.[5]

Brucella is a gram-negative intracellular bacteria transmitted to humans by direct contact with infected animals or by consumption of food products such as unpasteurized milk, cheese or undercooked meat.[2] Patients with brucellosis can present with multiple nonspecific symptoms like fever, chills, rigors, headache, arthralgia, myalgia and night sweats.[6] Focal infection with multiorgan involvement is not uncommon, and accounts for about 30 percent of cases.[7] Involvement of any system— bones, joints, genitourinary, pulmonary, cardiac and nervous system—has been reported.[1,8,9]

In our study, acute brucellosis was defined as the presence of typical symptoms for no longer than 7 days, subacute brucellosis as symptoms lasting more than a week but less than a month and chronic brucellosis as symptoms persisting for more than a month. Relapse of brucellosis was diagnosed if symptoms suggestive of brucellosis recurred within a year of treatment completion, with a concomitant rise in IgG using the 2-mercaptoethanol (2-ME) test. Persistence of high IgG is indicative of an active infection.[10,11] Cure was defined as resolution of symptoms, a fall in standard agglutination test (SAT) titers and clearance of bacteremia. Neurobrucellosis was diagnosed if neurological symptoms were associated with elevated protein, normal or low glucose concentration, lymphocytic pleocytosis and high *Brucella* SAT titers in the cerebrospinal fluid. *Brucella* endocarditis was diagnosed in symptomatic patients with vegetations on echocardiogram, along with significantly high SAT titers, 2-ME titers, or culture of *Brucella* organisms from blood. Organ abscess was diagnosed if imaging studies showed collection and culture of the aspirate-grown grew *Brucella* species.

There are several treatment regimens for brucellosis, which differ according to the organ involved, complications, cost and access to care.[12-18] The treatment recommended by the World Health Organization (WHO) for brucellosis in adults is rifampicin 600 to 900 mg daily and doxycycline 100 mg twice daily for a minimum of six weeks.[19] Another commonly recommended regimen is doxycycline combined with an aminoglycoside in the first two weeks of therapy.[15] Saudi Arabia is endemic for tuberculosis, and many experts avoid the use of rifampicin and aminoglycosides to reduce the emergence of rifampicin- and aminoglycoside-resistant *Mycobacterium tuberculosis* unless deemed essential as in the treatment of osteomyelitis, neurobrucellosis or endocarditis. Ciprofloxacin and co-trimoxazole are used as alternatives to rifampicin and aminoglycosides.[16,18]

A systematic review of treatment of brucellosis conducted by Alavi et al, demonstrated no differences in outcomes with the combination of doxycycline/ co-trimoxazole versus doxycycline/rifampicin.[15] A Cochrane review evaluated different drug regimens for treatment of brucellosis in terms of treatment failure and side effects: doxycycline plus rifampicin, doxycycline plus streptomycin, quinolones plus rifampicin or doxycycline plus gentamicin, and concluded that the incidence of total drug treatment failure was lower with doxycycline plus streptomycin than doxycycline plus rifampicin.[13] Some experts use a combination of three drugs in cases of bacteremic brucellosis.[15] In this study, we identified the various clinical manifestations of brucellosis and compared the efficacy of various combinations of antibiotics used in our institution to the WHO-recommended regimen of doxycycline/rifampicin in the treatment of brucellosis.

PATIENTS AND METHODS

A retrospective medical record review was done of patients diagnosed with brucellosis based on positive serology and or isolation of *Brucella* species from blood, body fluid or tissue, during the period from January 2003 to December of 2018. Patients were identified by searching the microbiology laboratory database at our institution to extract data on demographics, risk factors, signs and symptoms, end organ involvement, treatment regimens and outcomes, cure, residual defects, and relapse. Patients who had recurrence of symptoms within a year after treatment were included in the study a second time. Follow-up was performed for symptom resolution and trends in IgG and IgM titers at diagnosis 6 and 12 months after commencement of therapy.

The immune response in human brucellosis is characterized by an initial rise in IgM antibody titers that are followed within a few weeks by a switch to IgG synthesis. After treatment, titers decline with the levels of IgG falling more rapidly than IgM. The rapid fall in the level of IgG antibodies (2-ME test) is said to be prognostic of successful therapy, whereas a failure to decline or a subsequent rise in titer of IgG antibodies presages a clinical relapse.[10,11,18] The persistence of high serum an-

tibody titers in patients without relapse was mainly due to IgG and often associated with high titers at diagnosis or with focal disease.[10] At our center, laboratory diagnosis of brucellosis is made by blood culture using the fully automated BACTEC system (BD Company, New Jersey, United States) and the standard tube agglutination test (SAT). The SAT is used to measure the total agglutinating antibodies, IgG and IgM, to distinguish between immunoglobulin classes; 2-ME was added to reduce the disulfide bonds of the IgM pentamer, whereby the IgM molecule loses agglutinating activity while IgG is not affected. This differentiation is important because IgG antibodies are considered a better indicator of active infection than IgM antibodies.[20]

We included adults aged 14 years and older with a single significant IgG or IgM antibody titer (≥1:640) in the SAT, or a lower titer rising to significant levels, after two weeks, in the appropriate clinical settings, with or without isolation of *Brucella* species from blood, body fluids or tissue.

Based on the opinions of local experts, a higher titer of 1:640, rather than 1:320, is the cut-off used, as brucellosis is endemic.[20] The study was undertaken after obtaining approval from the Office of Research Affairs and the Research Promotion Committee of the hospital, and in accordance with the ethical principles of the Helsinki Declaration.

The data were examined for normality by visual inspection of histograms and the Kolmogorov-Smirnoff test. Descriptive statistics were calculated for each variable of interest, median for continuous variables, and number and percentage for categorical variables. Medians of antibody titers were presented and the differences across the two groups (cured versus relapsed) were tested for using the Mann- Whitney U test. All statistical analyses were performed using IBM SPSS version 20 for Windows (Armonk, New York, United States: IBM Corp).

RESULTS

Fever, arthralgia, and back pain were the most common presenting symptoms, occurring in 76 (62%), 47 (38%), and 42 (34%) cases, respectively (**Table 1**). Because it is routine practice to screen living-related donors of organs and the recipients for brucellosis and treat them before transplant even if asymptomatic, the 34 (28%) asymptomatic individuals who had significant SAT titers were treated. Of the individuals affected, 58(68 %) had a history of raw milk ingestion and 34 (52%) had a history of contact with animals.

In the 118 (96%) patients, the median IgG antibody titers at diagnosis and at 6 and 12 months were 1:1280,

Table 1. Demographic and clinical characteristics (n=123).

Age (years)	50 (15, 83)
Duration of symptoms before treatment (days)	30 (3, 1460)
Sex	
Male	85 (69)
Female	38 (31)
Contact with livestock	34 (52)
Consumption of raw milk	58 (68)
Previous treatment of brucellosis	
Yes	11 (9)
No	112 (91)
Positive blood culture	
Yes	50 (40)
No	73 (60)
Signs and symptoms	
Asymptomatic	34 (28)
Fever	76 (62)
Arthralgia	47 (38)
Night sweats	32 (26)
Arthritis	2 (2)
Back pain	42 (34)
Other symptoms	17 (13.8)
Fatigue and social isolation	1 (0.8)
Headache	2 (1.6)
Hearing loss and unsteady gait	1 (0.8)
Lower limb weakness	2 (1.6)
Parotid gland swelling	1 (0.8)
Productive cough, and shortness of breath	1 (0.8)
Psychiatric symptoms	1 (0.8)
Tinnitus, and dizziness	1 (0.8)
Weight loss	6 (6.4)
Focal complications	
None	98 (80)
Osteoarticular involvement	12 (9)
Long bone	1 (0.8)
Large joint	1 (0.8)
Vertebrae	10 (8.1)
Neurobrucellosis	5 (4.1)
Endocarditis/vegetation	5 (4.1)
Organ abscess (one liver, parotid, and lung each)	3 (2.4)

Data are number (%) or median (minimum, maximum) for age and duration of symptoms before treatment.

1:640, and 1:320, respectively, while the median IgM antibody titers were 1:1280, 1:640 and 1:160, respectively, clearly indicating resolution of the disease, while in 5 (4%) the median IgG antibody titers at diagnosis and at 6 and 12 months were 1:640, 1:2560, and 1:2560, respectively; while the median IgM antibody titers were 1:9600, 1:2560 and 1:7680, respectively (**Table 2**).

Blood cultures were positive in 50 (40%) patients, and among them, 32 (64%) were classified as subacute brucellosis. Repeat blood cultures at the end of treatment were negative. The major organs involved were the axial skeleton in 12 (9%), central nervous system in 5 (4%), and heart in 5 (4%). In our cohort, three patients presented with deep abscesses, one each in the liver, parotid gland and lungs (**Table 1**).

Neither duration of illness nor bacteremia were predictors of disease outcome. Eleven (9%) patients who had received treatment outside hospitals were cured with a second course of treatment at our institution. Compliance was excellent in 96% of patients, and only five patients (4%) had a documented relapse from self-reported non-adherence. All five patients responded to a second course of therapy.

Treatment with doxycycline/rifampicin was compared with doxycycline/co-trimoxazole, ciprofloxacin/doxycycline, a regimen with rifampicin other than doxycycline/rifampicin and any regimen that included aminoglycosides. There were no differences in outcome between the different regimens used in our cohort, as evidenced by a significant decrease in SAT titers and symptom resolution within six months. For patients who received doxycycline/rifampicin, the median IgM/IgG at diagnosis and at 6 and 12 months were 1:1260/1:320,1:640/1:160 and 1:160/1:80, respectively, while for the group treated with doxycycline and co-trimoxazole, the median IgM/IgG titers at diagnosis and at 6 and 12 months were 1:1590/1:1280,1:640,1:640 and 1:280/1:320, respectively.

DISCUSSION

In this retrospective study, the median age at presentation was 50 years, much older than that reported in other studies.[3,5] Disease was seen more frequently in men, as reported in other studies.[21,22] The majority of patients had comorbidities such as type 2 diabetes mellitus, chronic kidney disease, malignancy, and hypertension. Brucellosis infection in pregnant women results in adverse outcomes. Abortions, intrauterine fetal death, and preterm deliveries have been reported.[22,23] In our cohort, only one patient was pregnant and did well with co-trimoxazole and rifampicin. This combination is recommended in pregnant women between 12-36 weeks of gestation.[21] If gestational age is ≥36 weeks, rifampin monotherapy is used until delivery, due to the risk of neonatal kernicterus with co-trimoxazole, while teratogenicity is feared in the first trimester. Some experts use ceftriaxone with rifampicin during pregnancy, with good outcomes.[23]

Contact with cattle was identified in 34 (52%) patients who were engaged in animal husbandry, while 38

Table 2. Comparison of antibody titers in cured and relapsed patients.

	All patients (n=123)	Cured (n=118, 96%)	Relapsed (n=5, 4%)	*P* value
IgG				
At diagnosis	1280 (20-20480)	1280 (20-20480)	640 (640-20480)	.95
At 6 months follow up	640 (20-20480)	640 (0-20480)	2560 (40-20480)	.30
At 12 months follow up	320 (0-20480)	320 (0-20480)	2560 (40-20480)	.01
IgM				
At diagnosis	1280 (0-19840)	1280 (0-19840)	9600 (0-19840)	.31
At 6 months follow up	640 (0-20160)	640 (0-20160)	2520 (0-7680)	.72
At 12 months follow up	260 (10240-20160)	160 (0-20160)	7680 (10240-320)	.18
Total				
At diagnosis	5120 (320-20480)	5120 (320-20480)	20480 (1280-20480)	.19
At 6 months follow up	2560 (20-20480)	2540 (20-20480)	10240 (2560-20480)	.03
At 12 months follow up	640 (0-20480)	640 (0-20480)	10240 (320-20480)	.01

Data are median (minimum, maximum). Statistical analysis by the Mann-Whitney test for age, and the chi-square test for remaining comparisons of cured vs relapsed.

(58%) had consumed unpasteurized milk, which is still customary in Arab countries. These are the two most common risk factors for brucellosis, but with frequencies that vary depending on the population studied. The most common presentation in our cohort was fever and back pain, similar to that reported in several studies.[25] The 34 (28%) who were asymptomatic were identified on screening of living organ donors and recipients. The hospital guidelines for organ transplant include screening for all possible infections, including brucellosis.

Our study revealed no difference in cure rates between the WHO recommended regimen of doxycycline with either rifampicin or aminoglycoside, versus doxycycline with co-trimoxazole. However, larger randomized controlled trials are needed to confirm the efficacy of doxycycline/co-trimoxazole regimen. Falagas et al concluded in a systematic review that a quinolone-based regimen in combination with either rifampicin or tetracycline might have a comparable effect on the rate of disease relapse with fewer adverse effects.[24] The choice of regimen in our institution is individualized based on patient characteristics and severity of disease. The first choice of infectious disease physicians in our institution is the combination of doxycycline with co-trimoxazole in patients without focal disease, as most patients in our cohort were older than 50 years with comorbidities such as diabetes mellitus and chronic kidney disease.

Patients with spondylitis usually receive a combination of aminoglycosides and doxycycline. Aminoglycoside is typically administered in the first 2-3 weeks, with continuation of doxycycline to complete the total duration of 12 weeks.

In patients with *Brucella* bacteremia, some experts use three drugs in combination or a combination of doxycycline and aminoglycoside. A systematic review by Skalsky noted that a three-drug combination regimen of aminoglycoside, preferably gentamicin, for the first two weeks added to doxycycline/rifampicin for six–eight weeks resulted in the lowest relapse rate.[25]

In bacteremic patients, where aminoglycosides are contraindicated, a higher dose of co-trimoxazole double strength three times a day or co-trimoxazole double strength two tablets twice a day (trimethoprim 5-10mg/kg per day in divided doses) is preferred. Although some studies have shown relapse rates of over 40% with combinations using co-trimoxazole, our results showed no difference in efficacy nor higher relapse rate as compared to doxycycline/rifampicin, which is consistent with the conclusion of the systematic review by Alavi et al.[15] Use of rifampicin and streptomycin in treatment of brucellosis was a major contributor to the rising resistance of *M tuberculosis* in Saudi Arabia, and we recommend that use of rifampicin be restricted in the treatment of brucellosis.[16] Rifampicin use is also best avoided if a drug- drug interaction is expected (e.g. oral contraceptives, warfarin). Moreover, rifampicin is not freely available to physicians working in private clinics or hospitals in the country. Hence, it is vital to find effective treatment options for brucellosis that exclude rifampicin, and this study demonstrates that doxycycline with co-trimoxazole or quinolone is equivalent to doxycycline/rifampicin.

It is likely that the adherence to medications in our cohort was excellent, as the use of parenteral aminoglycoside was minimal. Individuals with major organ involvement, such as neurobrucellosis or endocarditis, were treated as inpatients to complete the aminoglycoside therapy.

In conclusion, doxycycline with co- trimoxazole is equivalent to doxycycline/rifampicin in efficacy and should be preferred in countries with a high prevalence of tuberculosis. Nonetheless, rifampicin should be part of the treatment regimen for neurobrucellosis and endocarditis and is the mainstay in pregnant women and children.[15,24,26,27] The limitations of this study were its retrospective nature and the relatively small number of patients. A prospective randomized study to compare the combination of doxycycline with either rifampicin, co-trimoxazole, or ciprofloxacin in patients without focal disease, and with a larger cohort, will provide a more definitive answer. Management of brucellosis remains a challenge because of its clinical manifestations, limited diagnostic tests and the propensity to relapse. The results of our study, based on local expertise, will serve as guidance for other practitioners in the country. Avoiding parenteral drugs, when feasible, can result in improved adherence and outcomes.

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