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CLINICAL PRESENTATIONS AND TREATMENT OUTCOMES OF CULTURE-POSITIVE BRUCELLOSIS

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Abstract:

Introduction: Brucellosis is one of the most common zoonotic infections worldwide. It is an important cause of economic loss and a public health problem in many developing countries. In Saudi Arabia, the most common species is B. melitensis that causes 80 -100% of cases. In this study, we aimed to identify the clinical presentations and treatment outcomes of brucellosis.

Methodology: This is study was conducted at the King Abdulaziz Medical city, Saudi Arabia. The study included all patients that were diagnosed as culture-positive Brucella from 2000 to 2018. The data were collected from the patients' files and electronic microbiology lab results.

Results: The study included 165 cases of culture-positive Brucella. Non-focal brucellosis was the most common presentation with a rate of 75.8%. However, brucellosis infecting the CNS was a rare presentation with only three (1.8%) patients. Doxycycline plus rifampicin was the mainstay of treatment, and 47.3% of patients received this regimen followed by streptomycin with doxycycline, which was administered to 14.5%, and 11.5% of the patients received a triple therapy including streptomycin, doxycycline, rifampicin. The improvement rate was detected among 69.7% of the patients and mortality rate of 2 cases (1.2%).

Conclusions: Brucellosis is a disease that is prevalent in our society and its prevalence has increased this decade compared to the previous one. There are different treatment regimens that can be used but the outcome is unpredictable with any choice. Doxycycline with rifampicin had the best improvement rate in our study compared to the other treatment regimens.

Key words: *Brucellosis; Malta fever; Saudi Arabia; treatment; outcome.*

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INTRODUCTION:

Brucellosis is a systemic infection caused by Brucella species, which is a non-spore forming, non-motile, gram-negative, aerobic coccobacillus [1]. These are facultative intracellular pathogens that can survive and multiply in macrophages and polymorphonuclear cells [2]. Four species are pathogenic for humans: Brucella abortus, B. melitensis, B. suis, and B. canis. Brucellosis is one of the most common zoonotic infections worldwide. It is an important cause of economic loss and a public health problem in many developing countries [3]. In Saudi Arabia, the most common species is *B.* melitensis that causes 80–100% of infection cases, and *B.* abortus is the least common species [4-6]. Brucellosis has high morbidity both for humans and animals. Further, there has been a steady increase in the incidence of brucellosis in Saudi Arabia. The study by Hassan *et al*. on the epidemiology of brucellosis in Saudi Arabia reported an infection rate of approximately 70 in every100, 000 people [7].

Brucellosis can involve any organ system, and it has a wide variety of presentations ranging from asymptomatic disease to severe or fatal illness [8]. However, focal infection occurs in approximately 30% of cases [9-10]. It includes non-specific symptoms such as fever, sweating, arthralgia, hepatomegaly, and splenomegaly. Focal infection affects the sacroiliac joint, peripheral joints, liver, lung, and the nervous system in 8%, 41.3%, 2.9%, 4.3%, and 4.3%, respectively [11]. The diagnosis of brucellosis is based on detection of the organism in blood or body tissues or the combination of suggestive clinical presentation and positive serology [12-13].

The treatment regimens and duration for brucellosis is controversial. Mono-therapies are associated with high rates of relapse. Therefore, a combination of two drugs is preferred [14]. Moreover, some drug combinations may be more effective than others. A meta-analysis study found that doxycycline and streptomycin, which successfully cured 92% of cases, was better than doxycycline and rifampicin, which successfully cured 81% of cases [15].

In this study, we analysed the clinical presentations and treatment outcomes of brucellosis in a tertiary care hospital in Jeddah, Saudi Arabia from 2000 to 2018. In addition, we identified the common presentations of culture-positive brucellosis and its response to different antibiotic regimens.

METHODOLOGY:

Study design

This is a retrospective study that was conducted in the National Guard Hospital at King Abdulaziz medical city, Jeddah, Saudi Arabia. In this study, we recruited patients who were diagnosed with culture-positive *Brucella* from 2000 to 2018. Brucellosis was diagnosed based on the presence of objective findings supporting the diagnosis of *Brucella* infection such as obtaining a positive culture from the blood, arthrocentesis, cerebrospinal fluid, or tissue biopsy.

Sampling technique

We included all patients diagnosed with culture-positive brucellosis from 2000 to 2018 who met the inclusion criteria.

Data collection methods, instruments used, measurements

We reviewed the patients' files and electronic microbiology lab results including serology test results, site of sample collection, culture results, and antibiotic susceptibility test, if performed.

We created a data collection sheet using Microsoft Excel. The sheet included the demographic data, date of diagnosis, comorbidities, type of intervention, and treatment outcome.

Statistical Analysis

Categorical variables were presented as counts and proportions (%) while continuous variables were presented as mean and standard deviation, whenever appropriate. Between comparison of variables, Fischer Exact or One-way Anova test were applied. P-value of ≤ 0.05 was considered statistically significant. All data analyses were performed using the Statistical Packages for Software Sciences (SPSS) version 21 Armonk, New York, IBM Corporation.

RESULTS:

This included 165 patients who had culture-positive brucellosis. As seen in Table 1, the mean age was 41.9 years (SD 21.9) with 60% were males. Of our sample, 83.6% of the cases had a completely sensitive *Brucella* species, while 5.4% were resistant to variety of medications with rifampicin being the most commonly resistance medication (3.6%). Furthermore, non-focal brucellosis was the most common infection compromising 75.8% of the cases; this was followed by joint (13.3%) and spine (3.1%). We also noted brucellosis infecting CNS was very rare (1.8%). Similarly, brucellosis was mostly cultured in the blood (84.2%) and the joint fluid (12.1%) while bone tissue was the least cultured (0.6%). The proportion of patients who had brucellosis history of medical prescription was 9.7%.

Likewise, associated comorbidities were discovered among brucellosis patients that includes; HIV (0.6%), diabetes (19.4%) and malignancy (8.5%). In addition, 4.2% of the patients were immunosuppressed.

The trend of brucellosis cases in each year between years 2000–2018 are shown in Figure 1. It was revealed that the highest cases were recorded in the year 2016, followed by 2017 and 2018 while the least cases were recorded during year 2013.

Figure 2 depicted the prescribed medication treatment. It demonstrated that the most commonly used drug regimen was doxycycline with rifampicin (47.3%), followed by streptomycin with doxycycline which was administered to 14.5%, and 11.5% of the patients received triple therapy including streptomycin, doxycycline, and rifampicin.

Regarding follow up and the outcome of the treatment, it was found that the treatment was completed in 120 out of 165 cases with an overall percentage of 72.7%. There were 37 (22.4%) patients who lost to follow up, while 5 (3%) patients did not complete treatment due to adverse effects and 3 (1.8%) were non-compliant. Overall, improvement was detected among 115 (69.7%) of the patients, 42 (25.5%) were inconclusive. Treatment failure occurred in 6 (3.6%) patients and two (1.2%) patients passed away due to brucellosis.

Table 2 describes the outcomes of patients with non-focal brucellosis. Those who received doxycycline with rifampicin had better improvement rate than the other medications, while rifampicin with augmentin deemed to be the least effective as none of the patients improved.

In regards to the three patients with CNS brucellosis, our analysis revealed that two patients received doxycycline, rifampicin, and ceftriaxone. Those patients' outcomes were inconclusive. The third patient was prescribed amikacin, doxycycline, rifampicin, and trimethoprim/sulfamethoxazole (TMP/SMX). This patient improved on treatment.

In Table 3, it was shown that resistance pattern have no significant differences with the overall outcome (X2=8.611; p=0.236). Similar observation was made concerning infection site (X2=14.621; p=0.292). Also, there was no significant relationship between the treatment regimen and the outcome (X2=30.440; p=0.233) as shown in Table 4.

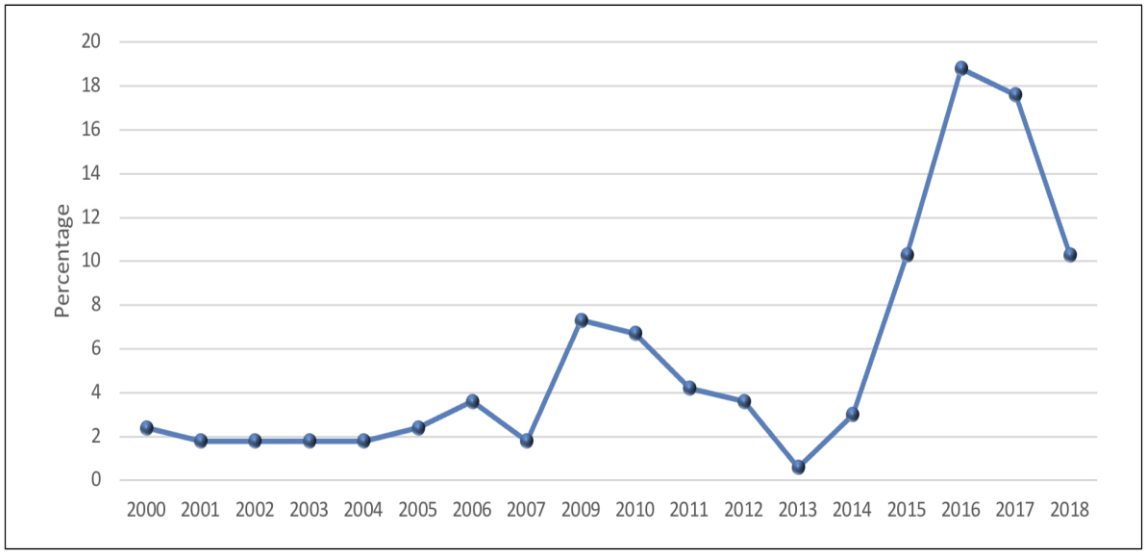

Figure 1. Trend of Brucellosis cases in each year.

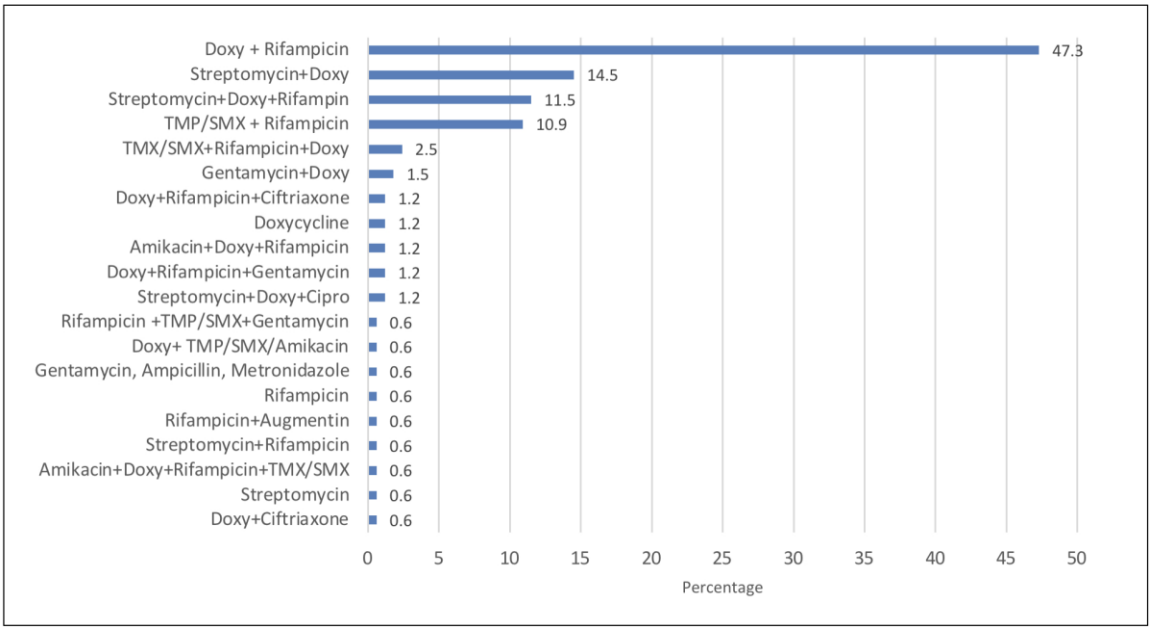

Figure 2. Prescribed medication regimens.

Table 1. Baseline characteristics of the patients (n=165)

Study variables	**N (%)**
Age in years (mean ± SD)	41.9 ± 21.9
Gender	
• Male	99 (60%)
• Female	66 (40%)
Sensitivity	
• Resistant to Ceftriaxone	1 (0.6%)
• Resistant to Gentamycin	1 (0.6%)
• Resistant to Rifampicin	1 (0.6%)
• Resistant to trimethoprim/sulfamethoxazole	6 (3.6%)
• Fully sensitive	138 (83.6%)
• Not known	18 (10.9%)
Infection site	
• Generalized (non-focal)	125 (75.8%)
• Joint	22 (13.3%)
• Spine	10 (6.1%)
• Central nervous system	3 (1.8%)
• Epididymis and testes	1 (0.6%)
• Soft tissue abscess	1 (0.6%)
• Osteomyelitis	1 (0.6%)
• Endocarditis	1 (0.6%)
• Septic abortion	1 (0.6%)
Culture site	
• Blood	139 (84.2%)
• Joint fluid	20 (12.1%)
• Spine tissue	1 (0.6%)
• Cerebrospinal fluid	4 (2.4%)
• Bone tissue	1 (0.6%)
Brucellosis history of medical prescription	
• Yes	16 (9.7%)
• No	125 (75.8%)

• Unknown	24 (14.5%)
Human immunodeficiency virus	
• Yes	1 (0.6%)
• No	113 (68.5%)
• Unknown	51 (30.9%)
Diabetes	
• Yes	32 (19.4%)
• No	87 (52.7%)
Unknown	46 (27.9%)
Malignancy	
• Yes	14 (8.5%)
• No	103 (62.4%)
• Unknown	48 (29.1%)
Immunosuppressed	
• Yes	7 (04.2%)
• No	105 (63.6%)
• Unknown	53 (32.1%)
Duration of symptoms in days (mean ± SD)	3.93 ± 8.66

Table 2. Treatment of generalized (non-focal) brucellosis and their outcome

Treatment of generalized Brucellosis	**Outcome**				**Total N (%)**
	Inconclusive N (%)	**Improved N (%)**	**Died N (%)**	**Treatment Failure N (%)**	
Doxycycline + Rifampicin	19 (50%)	43 (53.1%)	1 (50%)	2 (50%)	65 (52%)
Streptomycin + Doxycycline	11 (28.9%)	11 (13.6%)	1 (50%)	0	23 (18.4%)
Streptomycin + Doxycycline + Rifampin	4 (10.5%)	7 (8.6%)	0	0	11 (8.8%)
TMP/SMX + Rifampicin	3 (7.9%)	5 (6.2%)	0	0	8 (6.4%)
Gentamycin + Doxycycline	0	3 (3.7%)	0	0	3 (2.4%)
Streptomycin + Doxycycline + Ciprofloxacin	0	1 (1.2%)	0	1 (25%)	2 (1.6%)
Amikacin + Doxycycline + Rifampicin	0	2 (2.5%)	0	0	2 (1.6%)
Doxycycline	0	2 (2.5%)	0	0	2 (1.6%)
Doxycycline + Ceftriaxone	0	1 (1.2%)	0	0	1 (0.8%)
Streptomycin	0	1 (1.2%)	0	0	1 (0.8%)
Streptomycin + Rifampicin	0	1 (1.2%)	0	0	1 (0.8%)
Rifampicin + Augmentin	0	0	0	1 (25%)	1 (0.8%)
Rifampicin	0	1 (1.2%)	0	0	1 (0.8%)
Doxycycline + TMP/SMX + Amikacin	0	1 (1.2%)	0	0	1 (0.8%)
Rifampicin + TMP/SMX + Gentamycin	0	1 (1.2%)	0	0	1 (0.8%)
Doxycycline + Rifampicin + Gentamycin	0	1 (1.2%)	0	0	1 (0.8%)
TMX/SMX + Rifampicin + Doxycycline	1 (2.6%)	0	0	0	1 (0.8%)

TMX/SMX: trimethoprim/sulfamethoxazole

Table 3. Overall outcome regarding the pattern of resistance and site of infection

Infection site	Outcome				X2	P-value[§]
	Inconclusive N (%)	Improved N (%)	Died N (%)	Treatment Failure N (%)		
Resistance pattern						
• Ceftriaxone R	0	1 (1%)	0	0		
• Gentamycin R	1 (2.6%)	0	0	0		
• Rifampicin R	1 (2.6%)	0	0	0	8.611	0.236
• TMX/SMX R	0	6 (5.9%)	0	0		
• Fully sensitive	36 (94.7%)	95 (93.1%)	2 (100%)	5 (100%)		
Infection Site						
• Generalized	38 (90.5%)	81 (70.4%)	2 (100%)	4 (66.7%)		
• Joint	2 (4.8%)	19 (16.5%)	0	1 (16.7%)		
• Spine	0	9 (7.8%)	0	1 (16.7%)	14.621	0.292
• CNS	2 (4.8%)	1 (0.9%)	0	0		
• Others	0	5 (04.3%)	0	0		

[§] P-value has been calculated using Fischer Exact test.

Table 4. Comparison of the use of different brucellosis treatment regimens with the outcome (n=165)

Treatment improvement	Overall N (%)	Treatment Improve		X2	P-value [§]
		Yes	No		
Doxy + Rifampicin	78 (47.3%)	55 (47.8%)	23 (46%)		
Streptomycin + Doxy	24 (14.5%)	12 (10.4%)	12 (24%)		
Streptomycin + Doxy + Rifampicin	19 (11.5%)	15 (13.0%)	4 (8%)		
TMP/SMX + Rifampicin	18 (10.9%)	12 (10.4%)	6 (12%)		
Gentamycin + Doxy	3 (1.8%)	3 (2.6%)	0		
Streptomycin + Doxy + Cipro	2 (1.2%)	1 (0.9%)	1 (2%)		
Amikacin + Doxy + Rifampicin	2 (1.2%)	2 (1.7%)	0		
Doxy + Rifampicin + Ceftriaxone	2 (1.2%)	0	2 (4%)		
Doxycycline	2 (1.2%)	2 (1.7%)	0		
Doxy + Ceftriaxone	1 (0.6%)	1 (0.9%)	0		
Streptomycin	1 (0.6%)	1 (0.9%)	0		
Streptomycin + Rifampicin	1 (0.6%)	1 (0.9%)	0	30.440	0.233
Rifampicin + Augmentin	1 (0.6%)	0	1 (2%)		
Rifampicin	1 (0.6%)	1 (0.9%)	0		
Doxy + TMP/SMX/Amikacin	1 (0.6%)	1 (0.9%)	0		
Rifampicin + TMP/SMX + Gentamycin	1 (0.6%)	1 (0.9%)	0		
Gentamycin, Ampicillin, Metronidazole	1 (0.6%)	1 (0.9%)	0		
Doxy + Rifampicin + Gentamycin	2 (1.2%)	2 (1.7%)	0		
Amikacin + Doxy + Rifampicin + TMX/SMX	1 (0.6%)	1 (0.9%)	0		
TMX/SMX + Rifampicin + Doxy	4 (2.4%)	3 (2.6%)	1 (2%)		

[§] P-value has been calculated using Fischer Exact test.

DISCUSSION:

This study aimed to identify the main presentations of brucellosis and outcomes of treatment. The most common presentation was generalized (non-focal) disease (75.8%) followed by joint involvement (13.3%). Brucellosis affecting central nervous system was seen in only three patients. A wide variety of treatment combinations were used but doxycycline and rifampicin were the most common. The majority of the patients were cured from the disease, and the mortality rate was 1.2%. There was no statistical difference in the outcomes between different treatment regimens but doxycycline and streptomycin showed a lesser duration for symptoms resolution after starting treatment.

Brucella species, after entering the body, arrive at local lymph nodes through polymorphonuclear leukocytes and macrophages or via extracellular routes [16]. The release of bacterial endotoxin from phagocytic cells produces the constitutional symptoms and signs of the disease. This partly explains why not all febrile brucellosis patients have bacteremia and not all bacteremia patients are febrile [17]. Brucellosis is mainly transmitted to humans through contact with fluids from infected animals (sheep, camels, goats, or other animals) or from food products such as unpasteurized milk and cheese. The prevalence of human brucellosis correlates closely with that of animal infection. In 1977, the incidence of brucellosis in Makkah, Saudi Arabia was found to be 0.8%, 0.5%, 2.8%, and 3.6% in goats, sheep, camels, and cows, respectively [18]. In 1987, the incidence of brucellosis had increased to 18.2%, 12.3%, 22.6%, and 15.5% in goats, sheep, camels, and cows, respectively, in Asir region [4]. The incidence rate of brucellosis in Saudi Arabia is generally greater than developed countries and most of the developing countries. From 2004-2012, in Saudi Arabia, brucellosis risk was higher in male Saudi population between 15-44 years of age, as this population has more opportunity to contact with animals as they travel more. Also, this group has more chance to drink row milk during the spring and summer season [19]. In the central part, Al-Qassim has the biggest number of cases, while Asir in the south and Hail in the North are coming after [19]. In comparison to the other parts of Saudi Arabia, the western part has the lowest number of cases [19]. The reasons why brucellosis becomes rare among developed countries are the presence of routine domestic live stock screening, ensuring animal vaccination, and tough rules when it comes to animal importation. Another study aimed to survey the population of central region in Saudi Arabia to establish the prevalence of brucellosis. This study showed that, brucella antibodies were present in 48.5% of the involved population [20]. Active disease was present in 2.5%, which was evident clinically and serologically. Moreover, patient living in rural area are more likely to have the disease than those living in urban areas [20]. Although the rate of the seropositivity was higher in females compared to males, active disease affects both sexes equally. The peak of the active disease was in people between 40-59 years of age. [20]

Brucellosis can occur in all age groups. There were more cases in men than in women in our study due to the difference in risk exposure because of the cultural customs in raw milk intake. The outcome of brucellosis is favorable, but the increasing number of cases of brucellosis is alarming. During our study period, incidence increased in some years. Based on this, we can infer possible outbreaks that may have occurred at certain points in time. In our study, we noticed a relapse rate of approximately 9.7% based on the history of prior Brucella infection. TMP/SMX resistance was the most common and was observed in 3.6% of the cases, and this might be due to the overuse of the drug for community-acquired infections as compared to other drug regimens. Therefore, avoiding empirical use of TMP/SMX if alternative antibiotics can be used could help in decreasing resistance. None of the cases were resistant to more than one antibiotic, and only 5.4% of the cases were resistant to a single antibiotic. Therefore, we cannot determine the treatment outcome based on the resistance pattern. However, all treatment failure cases comprised only 3.6% of fully sensitive cases, and this may be due to the selection of antibiotic treatment regimens based on the culture and susceptibility results. Non-focal brucellosis was the most common infection site compromising to 75.8%; this was followed by joint then spine. We also noted CNS brucellosis was very rare (1.8%). Similarly, Brucellosis was mostly cultured in the blood and the joint fluid while bone tissue was the least cultured. Unlike previous studies, we found that all drug regimens had similar treatment outcomes, and no specific drug regimen was superior [14]. However, some of the drug regimens had slightly better outcome than other regimens in treating bacteremia and skeletal diseases. In this study, we found that those who took doxycycline with rifampicin had better improvement rate than the other treatment regimens while rifampicin with augmentin estimated to be the least effective as none of the patients improved. In our study, we found that the characteristics of the patients and their treatment

outcomes were similar to those reported previously [9-10].

CONCLUSION:

Brucellosis is a disease that is prevalent in our society and its prevalence has increased this decade compared to the previous one. There are different treatment regimens that can be used but the outcome is unpredictable with any choice. Doxycycline with rifampicin had the best improvement rate in our study compared to the other treatment regimens.

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