

ORIGINAL RESEARCH ARTICLE

Characteristics and outcomes of pediatric brucellosis cases collected from a tertiary academic hospital in Saudi Arabia

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Abstract

Brucellosis is a zoonotic disease caused by *Brucella* spp., affecting different body systems and leading to multiple complications. Although brucellosis is prevalent in several regions, including Saudi Arabia, limited research has focused on childhood brucellosis. This study aimed to characterize the features and outcomes of brucellosis in pediatric patients. We conducted a retrospective descriptive study involving children (<18 years) with confirmed brucellosis (diagnosed through culture, serology, or both) who received antibiotic therapy. Subjects were stratified into two groups based on age: younger (≤ 8 years) and older (> 8 years). We assessed treatment outcomes, including clinical cure, mortality, and hospital length of stay. A total of 20 patients were included, with 52.3% in the younger group and 47.7% in the older group. The majority were male (65%), with a mean age of 8.9 years, and 45% required hospitalization. Out of all the patients, only 6 (30%) reported consuming dairy products. Serologically, the baseline median antibody titers for *Brucella melitensis* and *Brucella abortus* were 1:1280 and 1:640, respectively. In the younger group, half reported arthralgia and presented with fever. While white blood cell elevation was not significant, C-reactive protein, erythrocyte sedimentation rate, and liver enzymes were elevated at baseline. The administered regimen varied, but about half of the patients received at least three antibiotics. All patients experienced clinical cures, and there were no deaths. This study highlights the characteristics of pediatric brucellosis in a country where the disease is endemic and provides evidence of positive prognosis associated with appropriate antibiotic therapy.

Keywords: Brucellosis; *Brucella*; Pediatric; Childhood; Zoonotic infection; Zoonosis

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1. Introduction

Brucellosis, also known as Mediterranean fever or Malta fever, is a common zoonotic infectious disease caused by *Brucella* spp., a genus within the family *Brucellaceae*, which includes 10 other species. *Brucella* spp. are small, non-spore, aerobic, non-motile Gram-negative intracellular coccobacilli.¹ The species most commonly implicated in human infections are *Brucella abortus*, *Brucella melitensis*, *Brucella suis*, and *Brucella canis*.² The first two species are the most prevalent in Saudi Arabia. The disease mainly

affects livestock animals; however, it can be transmitted to humans and causes serious complications if left untreated.

The principal signs and symptoms of brucellosis include fever accompanied by malaise, arthralgia, arthritis, weight loss, hepatosplenomegaly, and lymphadenopathy.^{2,3} The two primary risk factors for brucellosis are the consumption of raw, unpasteurized, or non-sterilized dairy products and direct contact with infected animals.² In pediatric patients, the main source of infection is the consumption of unpasteurized milk.^{3,4} The most frequent complications of brucellosis involve bone and joint tissues, occurring in up to 40% of cases.² Numerous uncommon complications of brucellosis have been described, such as cardiac complications (for example, endocarditis and myocarditis), testicular complications in male patients, and neurological complications such as meningitis and encephalitis. Brucellosis may also have ophthalmic complications. However, these are considered rare in pediatrics.⁴

The global annual incidence rate of human brucellosis is estimated at 2.1 million cases.⁵ The disease remains a major threat to human health in many developing countries, particularly in North and East Africa, the Mediterranean basin, and the Indian subcontinent.⁴ It is also endemic in the Middle East, the Arabian Peninsula, and parts of Central Asia and South America. On the contrary, human brucellosis has been eradicated from several developed countries, including many Northern European countries.⁴ In Saudi Arabia, the number of reported cases between 2004 and 2012 was 37,477, with the incidence risk significantly decreasing from 22.9 in 2004 to 12.5 in 2012. The Saudi cities with the highest percentage of cases are Alqassim, followed by Aseer, Hail, and the northern region,^{3,6} whereas the western region of Saudi Arabia has a lower incidence.⁴ In 2014, the Saudi Pediatric Infectious Diseases Society published clinical practice guidelines for brucellosis in children.⁷

Given that brucellosis is one of the most frequently reported diseases in Saudi Arabia and the limited number of published reports on childhood brucellosis, this study aimed to describe the characteristics, course of therapy, and outcomes of pediatric brucellosis cases in Saudi Arabia.

2. Materials and methods

2.1. Study design and patients

The current retrospective descriptive study was conducted at King Abdulaziz University Hospital, Jeddah, in the western region of Saudi Arabia. Data were collected from pediatric patients over 11 years, from January 2008 to February 2019. Ethical approval was obtained from the

Research Committee of the Unit of Biomedical Ethics, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia (approval reference no. 128-18).

Patients aged 18 years or younger at the time of brucellosis diagnosis, confirmed through blood culture and/or serology, were eligible for inclusion in the study. A list of patients was obtained using test codes for the *Brucella* antibody test and *Brucella* culture. Both paper and electronic medical records were reviewed to identify pediatric inpatient and outpatient patients (age <18 at the time of diagnosis).

2.2. Laboratory diagnosis

Patients included in this study had a confirmed diagnosis of brucellosis, either through a positive blood culture or an antibody titer for *B. abortus*, *B. melitensis*, or both, and received antibiotic treatment. The serological test used in our hospital was the serum agglutination test (SAT), which measured total antibodies (Immunoglobulin [Ig]G and IgM) and provided a semi-quantitative result (titer). Two types of antigens were used in the test – one for *B. abortus* and the other for *B. melitensis*. After mixing the antigen suspension with the patient's serum, the tubes were incubated at 37°C for up to 48 h. The test was validated using positive and negative controls supplied with the kit (different commercial tests were used). The SAT has a reported sensitivity of 95.6 – 100% and a specificity of 96 – 100%.^{8,9} In Saudi Arabia, where brucellosis is endemic, an antibody titer of at least 1:640 for either *Brucella* spp. is considered positive for confirming the diagnosis.

Microbiologically, blood samples from patients suspected of having brucellosis were labeled as “*Brucella*” and incubated at 37°C for up to 14 days in the BD BACTEC™ FX system (Beckton, Dickinson and Company, United States [US]). Positive samples were subcultured onto blood and chocolate agar plates, which were incubated for 24 – 48 h in a 5 – 10% CO₂ environment. If growth was observed on the plate, the bacteria were identified through the morphology of the colonies, Gram staining, and biochemical testing for urease and oxidase (as *Brucella* spp. produces both enzymes). While microbiological culture facilitated the identification of the genus *Brucella*, it does not provide species-level identification. The results from serological testing were used to identify the specific species.

2.3. Data collection

Collected data included demographics, clinical variables (including complications and organ or system involvement), date of admission (for inpatients), duration of hospital stay, antibiotic therapy administered, and

the date therapy ended. Clinical cure was defined as the complete resolution of brucellosis signs and symptoms, as documented in progress notes or outpatient visit records. Data were collected up to 3 months post-therapy completion, except for one patient whose data were only available after 8 months post-therapy. Patients were divided into two groups: younger patients (aged 8 years or younger) and older patients (aged older than 8 years). This stratification was based on the contradiction of doxycycline (an essential antibiotic in brucellosis treatment) in patients younger than 8 years and the more frequent occurrence of brucellosis-associated arthritis in the older age group.¹⁰⁻¹³

2.4. Statistical analysis

The collected data and laboratory results were presented descriptively using numbers, percentages, and mean \pm standard deviation. Statistical package (Statistical Package for Social Sciences version 24.0) (IBM Corp., US) was used.

3. Results

3.1. Characteristics of the patients

A total of 138 patients were screened for eligibility, of whom 20 met the inclusion criteria and were included in the study. Reasons for exclusions included duplicate records, age older than 18 years, no positive serology, positive blood cultures labeled with "*Brucella*" but did not yield *Brucella* spp., and no documented antibiotic treatment. Table 1 lists the demographics of included patients. The mean age was 8.9 years. About two-thirds were males (65%), and more than half were treated as outpatients (55%). The consumption of a dairy product was reported by 6 patients (30%), whereas the source of infection was unknown in the rest of the cohort. Upon presentation, about half (50%) of the patients complained of arthralgia and were febrile. Six of the 20 patients (30%) had elevated liver enzymes at baseline (three times the upper limit of normal; range 66 – 252 U/L for alanine transaminase [ALT] and 91 – 155 U/L for aspartate transaminase [AST]) that were decreased by the end of therapy by about 55% (range 33 – 64 U/L and 22 – 64 U/L for ALT and AST, respectively). Hepatosplenomegaly was noted in one patient, and splenomegaly was observed in another. Furthermore, two patients had complicated brucellosis (one had neurobrucellosis whereas the other had epididymo-orchitis), whereas the remaining 18 patients had uncomplicated brucellosis. Serological results revealed that 18 patients (90%) had antibodies against both *B. melitensis* and *B. abortus*, whereas the remaining two patients had antibodies against either species. Moreover, four patients had concurrent infections with other pathogens, including two cases of cytomegalovirus infection, one case of rheumatic fever, and one case of urinary tract infection.

3.2. Antibiotic regimens used

Antibiotic regimens varied significantly between the patients; however, most patients (53%) received a combination consisting of at least three antibiotics (Table 2). Most of the regimens in the younger group included rifampin and/or gentamicin with or without trimethoprim/sulfamethoxazole. On the other hand, the older group regimens consisted of rifampin and doxycycline alone or in combination with other agents.

3.3. End of therapy outcomes

Clinical outcomes data were available for 18 patients. All patients were clinically cured with no reported mortality (Table 3). In addition, temperature, white blood cell count, inflammatory markers, and liver enzymes were all normalized. Moreover, the average length of stay of hospitalized patients ($n = 9$) was 26 days, which was shorter in the older group (14.8 days) than in the younger group (34.4 days). With regards to antibody titers, they remained elevated in some patients but normalized in some, where the median (Interquartile range) was 1:320 (1:80 to 1:1280).

4. Discussion

Although brucellosis is a neglected disease worldwide, it poses a serious threat to public health in developing nations. Likewise, in Saudi Arabia, it continues to be endemic despite efforts to contain its spread. Any child experiencing a fever and having a history of consuming unpasteurized milk or animal contact should be evaluated for brucellosis.⁷ The primary objective of our study was to describe the characteristics and the clinical outcomes of childhood brucellosis in patients identified at our institution over 11 years.

In many countries, *Brucella* infection is an occupational disease, which makes it uncommon among children. However, this may not be the case in endemic regions where transmission occurs through non-occupational means. In our study, male patients outnumbered female patients (67% vs. 33%). One possible explanation could be that young male adults are more involved in outdoor activities and animal care. However, these findings disagreed with a national survey that linked female participation in animal milking to a greater infection risk among females.¹⁴ About a third of the patients had a history of consuming dairy products. This observation was consistent with the findings of a previous study conducted in Al-Khafji Joint Operation Hospital between 2011 and 2012, which reported raw animal milk ingestion as the major risk factor for brucellosis reported by up to 83% of pediatric patients.¹⁵ Consuming unpasteurized (or non-boiled) dairy products

Table 1. Patients' demographics

Characteristic	Total (n=20)	Younger group (n=9)	Older group (n=11)
Age (years)	8.9±5.1 (1 – 17)	4.5±1.9 (1 – 7)	10.1±2.9 (8 – 17)
Sex (male)	13 (65)	7 (77.8)	6 (54.5)
Location			
Outpatient	11 (55)	4 (44.4)	7 (63.6)
Inpatient medical ward	9 (45)	5 (55.6)	4 (36.4)
Temperature (°C)	37.9±1.1 (36 – 39.5)	37.9±1.2 (36 – 39)	37.9±0.9 (36.8 – 39.4)
White blood cell count, cells/mm ³	6.7±2.1 (3.3 – 10.6)	6±1.7 (3.3 – 8.9)	7.7±2.7 (5.2 – 10.6)
C-reactive protein (mg/L)	29±38.9 (3 – 169)	11.3±11.7 (3 – 39.7)	42.5±58.1 (3 – 169)
Erythrocyte sedimentation rate (mm/h)	33.8±19.5 (7 – 70)	38.8±23.4 (9 – 70)	28.6±15.5 (7 – 44)
ALT (U/L)	64.4±54.6 (12 – 252)	77.4±73 (19 – 252)	46.4±39.7 (12 – 116)
AST (U/L)	65.8±43.2 (8 – 155)	64.3±28.6 (27 – 102)	58.3±53.8 (8 – 152)
Risk factors for infection			
Consumption of unpasteurized dairy products	6 (30)	3 (33.3)	3 (27.3)
Unknown	14 (70)	6 (66.7)	8 (72.7)
Diagnostic test positivity			
<i>Brucella</i> serology alone	10 (50)	4 (44.4)	6 (54.5)
Both <i>Brucella</i> serology and culture	10 (50)	5 (55.6)	5 (45.5)
<i>Brucella</i> spp.			
<i>B. melitensis</i>	1 (5)	1 (11.1)	0 (0)
<i>B. abortus</i>	1 (5)	0 (0)	1 (9.1)
Both	18 (90)	8 (88.9)	10 (90.9)
Presence of co-infection	5 (25)	1 (11.1)	4 (36.4)
Presence of arthralgia	10 (50)	4 (44.4)	6 (54.5)
<i>B. melitensis</i> antibody titer	>1:1280 (1:640 – >1:1280)	>1:1280 (1:480 – >1:1280)	>1:1280 (1:640 – >1:1280)
<i>B. abortus</i> antibody titer	1:640 (1:320 – >1:1280)	1:640 (1:320 – >1:1280)	>1:1280 (1:640 – >1:1280)

Notes: Data are presented as mean±SD (range) or n (%), except for the antibody titers, which are presented as median (interquartile range).

Abbreviations: ALT: Alanine transaminase; AST: Aspartate transaminase; *B. abortus*: *Brucella abortus*, *B. melitensis*: *Brucella melitensis*.

is considered the major mode of zoonotic transmission of brucellosis to humans.^{2,5}

Brucellosis is a multisystem disease with a broad spectrum of non-specific signs and symptoms. This study found that fever and arthritis or arthralgia were the predominant presenting signs of the disease. This finding was in line with previous studies from endemic areas, such as Iran.¹⁶ Moreover, brucellosis-associated arthritis was previously reported in children older than 8 years.^{11-13,17} Although 48% of cases were detected only by the SAT serological tests, doctors are advised to have a high index of suspicion for *Brucella* culture since the symptoms in children might be mistaken for septic arthritis. In areas where brucellosis is widespread, such as Saudi Arabia, persistent exposure to the source of infection increases the titer value in which brucellosis is said to be established as a disease. In such areas, a titer of 1:640 or higher is a

good indicator of the presence of the disease, along with signs and symptoms compatible with *Brucella* arthritis in a community where *Brucella* is common.

Brucellosis could also affect any organ or system. Apart from two patients who had organ involvement – one had neurobrucellosis, and the other had testicular involvement – the current study revealed that the majority of patients had uncomplicated brucellosis. Notably, neurobrucellosis is not common among children, with an epidemiological study reporting an incidence of only 1% among children with brucellosis.¹¹ Although *Brucella* spp. can cause endocarditis and urinary tract infections,^{2,18,19} the reported cases of rheumatic fever and urinary tract infections were caused by pathogens other than *Brucella* spp.

Our study reported that 52% of the patients were diagnosed using the SAT along with blood *Brucella* culture. A recent study reported a lack of correlation between

Brucella serology and culture at baseline; therefore, clinicians must base their diagnosis on the clinical picture of the disease and use the culture and/or the serology as a guide to confirm the diagnosis.²⁰ In our study, leukopenia and thrombocytopenia were the hematological abnormalities that our patient cohort experienced during the active course of brucellosis. Moreover, only 10 of the 20 patients had elevated liver transaminases. These findings are consistent with earlier studies.²¹ It should

Table 2. Antibiotic regimens used (in descending order of the number of patients)

Regimen	Age group	n
Aminoglycoside+trimethoprim/sulfamethoxazole+rifampin	Younger group	3
Aminoglycoside+trimethoprim/sulfamethoxazole	Younger group	3
Doxycycline+trimethoprim/sulfamethoxazole+rifampin+ceftriaxone	Older group	2
Doxycycline+rifampin+ciprofloxacin	Older group	2
Doxycycline+rifampin	Older group	2
Aminoglycoside+doxycycline+rifampin+ceftriaxone	Older group	1
Aminoglycoside+trimethoprim/sulfamethoxazole+ceftriaxone	Younger group	1
Trimethoprim/sulfamethoxazole+rifampin	Younger group	1
Trimethoprim/sulfamethoxazole+rifampin	Older group	1
Doxycycline	Younger group	1

Notes: The younger group includes those who were ≤ 8 years old, whereas the older group includes those who were > 8 years old. Three patients received treatment as indicated in their medical records, but antibiotics were not identified.

Table 3. End-of-therapy outcome variables

Outcome	Total (n=20)	Younger group (n=9)	Older group (n=11)
Temperature ($^{\circ}\text{C}$)	36.8 \pm 0.2 (36.5 – 37)	36.7 \pm 0.3 (36.5 – 37)	36.8 \pm 0.2 (36.5 – 37)
White blood cells count (cells/mm ³)	7 \pm 2 (3.1 – 9.9)	6.9 \pm 2.3 (3.1 – 9.6)	7.1 \pm 1.7 (4.9 – 9.9)
C-reactive protein (mg/L)	4.9 \pm 2.9 (3 – 13.1)	5 \pm 1.8 (3 – 7.8)	4.8 \pm 3.5 (3 – 13.1)
Erythrocyte sedimentation rate (mm/h)	14.8 \pm 13.3 (3 – 42)	16.7 \pm 17.4 (3 – 42)	12.2 \pm 4.4 (8 – 17)
ALT (U/L ^a)	28.4 \pm 11 (12 – 46)	32.1 \pm 10.6 (17 – 46)	23.5 \pm 10.3 (12 – 39)
AST (U/L ^a)	29.7 \pm 16.7 (9 – 64)	36.6 \pm 17.9 (17 – 64)	20.5 \pm 10 (9 – 35)
<i>Brucella melitensis</i> antibody titer (median [IQR]) ^b	1:320 [1:80 – >1:1280]	1:240 [1:80 – >1:1280]	1:320 [1:80 – >1:1280]
<i>Brucella abortus</i> antibody titer (median [IQR]) ^b	1:320 [1:80 – >1:1280]	1:200 [1:80 – >1:1280]	1:640 [1:80 – >1:1280]
Days of therapy ^c	45.7 \pm 32 (7 – 120)	40 \pm 22.3 (7 – 72)	51.4 \pm 40 (7 – 120)
Length of stay ^d	25.7 \pm 19.6 (7 – 67)	34.4 \pm 22 (9 – 67)	14.8 \pm 9.8 (7 – 29)

Notes: Data are presented as (mean \pm SD, range) unless otherwise specified. Data are presented as mean \pm SD (range) or n (%), except for the antibody titers, which are presented as median (interquartile range). ^aData were available from 14 patients (eight in the younger group and six in the older group). ^bData were available from 15 patients (eight in the younger group and seven in the older group). ^cData were available from 18 patients (nine in the younger group and nine in the older group). ^dData were available for the nine admitted patients (five in the younger group and four in the older group).

Abbreviations: ALT: Alanine transaminase; AST: Aspartate transaminase; IQR: Interquartile range; SD: Standard deviation.

be noted that SAT has a reported high sensitivity rate of 93% – 100%, indicating a low likelihood of reporting false-negative results.²² However, false-positive results can occur as a result of cross-reactions with antibodies to other Gram-negative bacteria, such as *Salmonella* spp. and *Yersinia* spp.²² In our hospital, the speciation of *Brucella* is done using serological tests, where all the patients in our current cohort had SAT done for them. Interestingly, however, 18 (90%) of the patients tested positive for both *B. melitensis* and *B. abortus* antibodies compared with two patients who tested positive for either of the two species. Some potential explanations for this observation include co-infection by both species, previous exposure to one of the two species and then developing a new infection by the other since *Brucella* antibodies could persist for years,²³ or cross-reactivity due to overlapping epitopes of *Brucella* antigens leading to a false-positive result for multiple species.²⁴ The first two explanations could be attributed to the endemicity of the disease in Saudi Arabia.

Brucellosis should be treated using a combination therapy; otherwise, patients would be at high risk for relapse or treatment failure.^{7,25} In this study, the relapse rate was very low at 1%, and no fatality has been reported. In addition, the patients were successfully treated by the various regimens used. The most commonly prescribed regimens were those comprised of an aminoglycoside, trimethoprim/sulfamethoxazole, and rifampin, as well as a regimen comprised an aminoglycoside with trimethoprim/sulfamethoxazole. The former regimen has been recommended in the Saudi guidelines for patients < 8 years.⁷ Of note, ciprofloxacin and doxycycline were only

prescribed to patients older than 9 years (except for one 4-year-old who was given doxycycline). Recent evidence suggests that doxycycline can be safely given to children and pregnant women.²⁶ A thorough retrospective analysis of 1843 newborns with prenatal doxycycline exposure revealed no greater risk of birth defects or teratogenic risks when compared to those who were not exposed.²⁷ These findings suggest that the advantages of doxycycline use in young patients may outweigh the possible risks when treating specific diseases without effective alternatives or when doxycycline is considered the treatment of choice, as in the case of brucellosis.²⁸

Ciprofloxacin may be beneficial for brucellosis in cases of drug resistance when used in combination with rifampin.^{29,30} The patient who had neurobrucellosis was treated with a combination of doxycycline, trimethoprim/sulfamethoxazole, and ceftriaxone. Per a previous report, doxycycline and trimethoprim/sulfamethoxazole have been found to be effective in neurobrucellosis.³¹ Furthermore, third-generation cephalosporins with the ability to diffuse through the central nervous system, such as ceftriaxone, have shown good *in vitro* activity against isolates of *B. melitensis*.³² The Saudi guidelines recommend a regimen of doxycycline, trimethoprim/sulfamethoxazole, and rifampin to treat neurobrucellosis. They also discussed the advantages of using ceftriaxone in the initial therapy of neurobrucellosis in children older than 8 years.⁷

In our study, even though a clinical cure was achieved, the patient's antibody titers persisted after treatment was completed. The results of an earlier retrospective investigation that found that *Brucella* serology did not correlate with clinical outcomes at the end-of-treatment follow-up provide an explanation for this. Consequently, rather than depending exclusively on serological results during follow-up, clinicians should take into account the full clinical picture of the brucellosis patient and evaluate the attainment of a clinical cure based on the disappearance of baseline signs and symptoms.²⁰

This study has a few limitations. As a retrospective study, some data were unavailable. It was also conducted in a single center and included a small sample size; thus, the results might not be generalizable.

5. Conclusion

Our study described the characteristics of children diagnosed with brucellosis in an academic hospital, highlighting typical signs and symptoms of fever, arthralgia, and elevated liver enzymes. We emphasize that using a combination of at least two antibiotics effective against *Brucella* spp. is important for ensuring clinical success.

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Conflict of interest

Abrar K. Thabit is an Editorial Board Member of this journal but was not in any way involved in the editorial and peer-review process conducted for this paper, directly or indirectly. Separately, other authors declared that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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Ethics approval and consent to participate

Ethical approval was obtained from the Research Committee of the Unit of Biomedical Ethics, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia (reference no. 128-18), who waived the need for informed consent.

Consent for publication

As this was a retrospective study (old data of patients who have been discharged from the hospital), such consent was not obtained and could not be obtained given the nature of the study.

Availability of data

Data are available from the corresponding author upon request.

Further disclosure

The study abstract was published in the abstract book of the European Congress of Clinical Microbiology

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