

Clinical Presentations of Brucellosis Over a Four-Year Period at Sultan Qaboos University Hospital and Armed Forces Hospital, Muscat, Oman

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ABSTRACT: Objectives: Brucellosis is a highly contagious zoonotic disease which can have serious health implications for affected humans and livestock. This study aimed to evaluate the clinical presentation, geographical distribution and risk factors of brucellosis cases admitted over a four-year period to two hospitals in Muscat, Oman. **Methods:** This observational study was conducted from January 2015 to December 2018 at the Sultan Qaboos University Hospital and Armed Forces Hospital in Muscat. All patients with probable or definitive diagnoses of brucellosis according to the diagnostic criteria of the World Health Organization were included. Relevant data were gathered from the patients' medical records, including results from standard agglutination tests, Brucella enzyme-linked immunosorbent assays, bacterial blood or tissue/aspirate cultures and Brucella polymerase chain reaction tests. **Results:** A total of 64 patients were diagnosed with brucellosis over the study period. The median age was 31.5 years and 73.4% were male. The majority (95.2%) presented with fever, followed by weight loss (51%), transaminitis (48.4%), peripheral arthritis/arthralgia (15.9%) and back pain (spondylodiscitis/sacroiliitis; 23.4%). Overall, 75.5% reported having consumed raw dairy products, while only 25.9% gave a positive history of animal contact. **Conclusion:** Patients with brucellosis presented with a wide range of clinical features, the most predominant of which was fever. The majority of patients were residents of or had recently visited Salalah and had consumed raw dairy products. These findings highlight the need for healthcare practitioners to maintain a high index of suspicion for this diagnosis. Moreover, further regulatory measures are necessary to oversee the sale of raw/unpasteurised dairy products.

Keywords: Brucellosis; Bacterial Infections; Zoonotic Bacterial Infections; Risk Factors; Epidemiology; Oman.

ADVANCES IN KNOWLEDGE

- The findings of the study indicated that patients with brucellosis presented with a wide range of clinical features, the most common of which was fever.
- In addition, the results indicated that the primary source of infection was food-borne in nature.
- To the best of the authors' knowledge, this is the first study to report information regarding cases of human brucellosis in adult patients from various regions of Oman.

APPLICATION TO PATIENT CARE

- Based on these findings, clinicians should maintain a high index of suspicion of brucellosis among patients with such presentations in order to avoid unnecessary delays in diagnosis and treatment.
- Moreover, relevant information should be elicited during history-taking with regard to exposure to raw dairy products.

BRUCELLOSIS IS AN ENDEMIC BACTERIAL disease which affects wild and domestic animals all over the globe, principally cattle, goats, sheep, swine and camels.¹ Annually, more than 500,000 cases of zoonotic infection in humans are reported worldwide, particularly in certain regions such as the Mediterranean, Middle East, Africa and Latin America.^{1,2} The disease is known under various names in different parts of the world, including undulant fever, Malta fever and Mediterranean fever.³ In the Dhofar region of Oman, it is known as *maradh alhayawan*, meaning "disease of animals".

Brucellosis is caused by *Brucella*, a genus of small non-motile Gram-negative *coccobacilli* first isolated in 1886 by Scottish army surgeon, Sir David Bruce.⁴ Of the

seven known *Brucella* species, four are pathogenic to humans, namely *Brucella melitensis*, *B. abortus*, *B. suis* and *B. canis*. Human acquisition of the disease occurs via the consumption of raw milk or dairy products from unpasteurised milk and undercooked meat, as well as contact with fluids from infected animals.⁵ Airborne transmission has also been reported, especially in laboratory personnel.⁶ While human-to-human transmission is unusual, rare cases have been reported as a result of blood transfusion, bone marrow transplantation or sexual contact.^{7–10}

In animals, brucellosis causes mastitis, spontaneous abortions, stillbirths and premature infertility.^{1,2} In humans, brucellosis causes a systemic infection with a highly variable incubation period

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ranging from five days to a few months.¹¹ Patients can be clinically asymptomatic, with the infection detected solely upon screening by positive serological findings or can present with a wide spectrum of clinical features that are acute (<8 weeks), subacute (8–52 weeks) or chronic (>52 weeks) in duration. Focal disease occurs in approximately 30% of patients and can affect any organ.^{12,13} In particular, non-specific symptoms—such as fever, night sweats, *malaise*, weight loss, arthralgia and lymphadenopathy—or features mimicking other diseases can lead to delays in diagnosis and treatment, thus necessitating a high index of suspicion.¹⁴

The current study aimed to determine the clinical presentation, geographical distribution and epidemiological risk factors of brucellosis cases admitted over a four-year period to two hospitals in Muscat, Oman. Such information may prove useful to help policymakers address the disease in a concerted manner including the implementation of public awareness campaigns. In addition, regulatory instruments may also be important to detect and contain cases amongst farm animals in order to reduce the reservoir of infection. Moreover, an understanding regarding the wide spectrum of clinical presentations of this disease may encourage healthcare practitioners to include brucellosis in the differential diagnosis of patients with similar symptoms.

Methods

This observational study was conducted between January 2015 and December 2018 at the Sultan Qaboos University Hospital (SQUH) and Armed Forces Hospital (AFH) in Muscat. Initially, data collection was conducted on a retrospective basis for all cases diagnosed in 2015 and 2016. Subsequently, over the remaining two years, the study was conducted prospectively. The inclusion criteria comprised all patients with probable or definitive diagnoses of brucellosis according to the diagnostic criteria of the World Health Organization.¹⁵ Patients of all nationalities and both genders over 12 years of age were included in the study. Cases that had been diagnosed before January 2015 but were on treatment during the period of study were excluded.

Patients underwent serological testing with standard agglutination tests (SATs) using stained suspensions for *B. abortus* and *B. melitensis* (Remel Inc., San Diego, California, USA), with SAT titres of ≥ 1 in 160 considered positive. Cases of suspected relapse or chronic brucellosis were tested using a *Brucella* immunoglobulin (Ig) G and IgM enzyme-linked immunosorbent assay (ELISA). Blood culture samples from suspected brucellosis cases were incubated

aerobically for a total of 21 days using either the BacT/Alert® 3D microbial detection system (bioMérieux SA, Marcy-l'Étoile, Lyon, France) at AFH or the BD BACTEC™ blood culture system (Becton, Dickinson and Co., Franklin Lakes, New Jersey, USA) at SQUH. Sterile site samples were incubated for at least 14 days after plating them on culture plates that included 5% horse blood agar and incubated in aerobic atmospheric conditions.

Grey-coloured colonies of 1–2 mm in diameter demonstrating positive reactions to oxidase, catalase and urease and grown on blood and/or chocolate blood agar plates were considered characteristic of *Brucella* species, especially when the patient had also received positive SAT results. An additional growth characteristic was a faint growth after one day of incubation that gradually became more pronounced after two days. Under microscopy, the appearance of Gram-negative cocci or coccobacilli in Gram-stained blood cultures and Gram staining of colonies grown from sterile site sample cultures were deemed additional evidence. In general, speciation of the bacteria was not determined as this had no impact on patient management.

Data were analysed using Microsoft Excel version 16.48 (Microsoft, Redmond, USA). Descriptive analysis of data is presented as numbers and percentages.

This study was approved by the individual institutional research and ethics committees of SQUH (MERC#1890) and AFH (FMC-MEC 001/2019).

Results

A total of 64 patients were diagnosed with brucellosis over the study period, of which 36 (56.3%) presented to SQUH and 28 (43.8%) to AFH. The male-to-female ratio was 47:17 and the median age was 31.5 years (range: 14–71 years). Overall, six patients (9.4%) were diagnosed in 2015, 27 (42.2%) in 2016, 20 (31.3%) in 2017 and 11 (17.2%) in 2018. The diagnosis was made from positive blood cultures alone in three patients (4.7%), positive serology alone in 23 patients (35.9%) or from both positive blood cultures and serology in 34 patients (53.1%). Blood cultures were positive in 41 patients (73.2%), serology was positive in 59 patients (93.7%). Blood cultures and serology were not done on 8 and 1 patients respectively. Three patients (4.7%) grew the bacteria from synovial fluid of the affected knees [Table 1].

Of these, two patients who had unilateral septic arthritis also had positive blood cultures and serology. The third patient presented with bilateral septic arthritis of prosthetic knee joints. Blood cultures were also positive in all three patients but serology was

Table 1: Type of diagnostic test performed among cases of brucellosis presenting over a four-year period to the Sultan Qaboos University Hospital and Armed Forces Hospital, Muscat, Oman (N = 64)

Diagnostic test	n (%)		ND
	Positive	Negative	
Blood cultures (n = 56)*	41 (73.2%)	15 (26.8%)	8
Serology (n = 63)*	59 (93.7%)	5 (8%)	1

ND = not done. *Brucella grew in synovial fluid of three patients. All three had positive blood cultures but serology was positive in two only.

negative in one.

In terms of risk factors, 40 patients (75.5%) had a history of consumption of raw dairy, one of which was in the form of *kami*, 15 patients (25.9%) a history of animal contact and data were missing for 17 patients (11 for dairy consumption and 6 for animal contact) [Table 2]. With regards to location, 24 patients (37.5%) were from Al Batinah, particularly the town of Al-Musannah. A total of 17 (26.6%), eight (12.5%), eight (12.5%), five (7.8%) and two (3.1%) patients were from the Muscat, A'Sharqiyah, Ad Dakhiliyah, Dhofar and Al Wusta regions, respectively. However, 14 patients (21.9%) originally from outside the Dhofar region had acquired the infection during recent trips to Salalah where they had consumed raw dairy products from either street vendors (92.9%) or their local hosts (7.1%). In addition, two patients (3.1%) had acquired the infection in Europe and one (1.6%) in Saudi Arabia [Table 3].

The most common presentation was fever in 59 patients (95.2%), lasting for three weeks or longer in 41 cases (66%) and with associated night sweats, generalised fatigue and weight loss without any focal symptoms in 34 cases (57.6%). Transaminitis was observed in 30 patients (48.4%), while weight loss—either in terms of a measured amount lost or as a visual observation—was reported by 25 patients (51%). Back pain was reported in 15 cases (23.4%). Three patients had radiological evidence of sacroiliitis, 8 of spondylodiscitis and 4 had normal spinal MRI. Radiculopathy occurred in two patients (3%) [Table 4].

Table 2: Risk factors identified among cases of brucellosis presenting over a four-year period to the Sultan Qaboos University Hospital and Armed Forces Hospital, Muscat, Oman (N = 64)

Factor	n (%)	
	Yes	No
Consumption of raw dairy products (n = 53)*	40 (75.5)	13 (24.5)
Animal contact (n = 58) [†]	15 (25.9)	43 (74)

*Data of 11 patients were missing. [†]Data of six patients were missing

Table 3: Geographical distribution of cases of brucellosis presenting over a four-year period to the Sultan Qaboos University Hospital and Armed Forces Hospital, Muscat, Oman (N = 64)

Region	n (%)		
	No recent trip to Salalah (n = 50)	Recent trip to Salalah* (n = 14)	Total
Al Batinah	20 (40)	4 (28.6)	24 (37.5)
Muscat	11 [†] (22)	6 (42.9)	17 (26.6)
A'Sharqiyah	7 (14)	1 (7.1)	8 (12.5)
Ad Dakhiliyah	5 [‡] (10)	3 (21.4)	8 (12.5)
Dhofar	5 (10)	0 (0)	5 (7.8)
Al Wusta	2 (4)	0 (0)	2 (3.1)

*Including 13 cases that had consumed raw dairy products from street vendors and one case who had consumed raw dairy product(s) from their local host. [†]Including two cases who reported a recent history of consumption of raw dairy products in Europe, one from a tour around Europe including Turkey and the other in Bosnia. [‡]Including one patient who reported a recent history of consumption of raw dairy products in Saudi Arabia.

Peripheral arthritis/arthralgia was reported in 10 cases (15.9%), including four cases of hip arthritis, three of knee arthritis, one of both knee and elbow arthritis and four cases of knee arthralgia. One of the knee arthritis cases demonstrated involvement of the bilateral prosthetic knee joints. Genitourinary involvement in form of prostatitis or epididymo-orchitis occurred solely in six patients of the 47 male patients (12.8%). Respiratory manifestations were

Table 4: Clinical presentations of cases of brucellosis presenting over a four-year period to the Sultan Qaboos University Hospital and Armed Forces Hospital, Muscat, Oman (N = 64)

Presentation	n (%)
Fever	59 (95.2)*
Transaminitis	30 (48.4)*
Weight loss	25 (51) [†]
Back problems	15 (23.4) [‡]
Peripheral Arthritis	10 (15.9) [§]
Jaundice	8 (12.5)
Hepatosplenomegaly	7 (10.9)
Genitourinary problems	6 [¶] (12.8) ^{//}
Pancytopenia	5 (7.8)
Respiratory problems	5 (7.8)

*Not assessed in two cases. [†]Not assessed in 15 cases. [‡]Including four cases of lower back pain without radiological evidence, two of sacroiliitis, two of cervical spondylodiscitis, one of thoracic spondylodiscitis and six of lumbar spondylodiscitis. [§]Not assessed in one case. [¶]All six patients were male. ^{//}Not assessed in 17 cases, all of whom were females.

present in five patients (7.8%) in the form of dry cough; chest radiographs showed lung nodules in one patient, but were normal for the remaining four patients. Jaundice was present in eight patients (12.5%) and hepatosplenomegaly in seven (10.9%). Five patients (7.8%) had pancytopenia.

Among those without leukopenia, white cell counts for lymphocytes, neutrophils and monocytes were within normal range and remained so throughout treatment. For eight patients (17%), the erythrocyte sedimentation rate (ESR) at presentation was normal; however, this was not assessed in 17 patients. For the remaining 39 patients (83%), the median ESR was 45 mm/hour (range: 20–109 mm/hour). Levels of C-reactive protein (CRP) at presentation were not assessed in 10 cases and were normal in two patients (3.7%). For the remaining 52 patients (96.3%), the median CRP level was 58 mg/dL (range: 10–175 mg/dL). None of the patients presented with cardiac or neuropsychiatric manifestations.

Relapses occurred in seven patients (10.9%), including one patient with no known risk factors and two who once again consumed raw dairy products. No relevant history was documented for the remaining four patients. All relapses were confirmed via positive serology results, with four also having positive blood cultures. Although an attempt was made to measure the rate of serological positivity with treatment, sequential serology was performed in only 17 cases (26.6%). In these patients, the drop in positive serology occurred slowly, taking approximately two months to halve from 1/1,280 to 1/640 and up to a year to halve again from 1/320 to 1/160.

Discussion

The aim of the current study was to investigate the clinical presentation of cases of brucellosis admitted over a four-year period to two hospitals in Oman, along with their geographical distribution and any risk factors involved in the acquisition of the disease. According to official data from the Ministry of Health, brucellosis is a common zoonotic disease in Oman.¹⁶ An extensive serological survey of four species of domestic animals conducted from 1985–1986 showed high levels of *Brucella* seropositivity, predominantly in the Dhofar region.¹⁷ Overall, 95–99% and 81% of previous cases of brucellosis reported between 1998–2002 and 2013–2017, respectively, originated from the Dhofar region.^{16,18}

Similarly, the results of the present study show that the Dhofar region played an important role in the geographical distribution of brucellosis cases between 2015–2018, not only for local residents but

also for visitors. In particular, Salalah, the largest city in Dhofar, is an immensely popular tourist destination, particularly during the annual *Khareef* (monsoon) season from June to September due to its cool climate and lush landscape. In the current study, the greatest number of brucellosis cases per year were seen in 2016, a finding which could reflect the high number of visitors to Salalah in this year compared to those immediately preceding or following (652,986 visitors in 2016 versus 514,777 and 644,931 visitors in 2015 and 2017, respectively).¹⁹ However, this difference in numbers is too low to come to a strong conclusion.

The leading cause of human brucellosis cases worldwide is believed to be the transmission of *B. melitensis* in contaminated sheep and goat milk.⁵ However, patients acquiring brucellosis in Salalah are more likely to have acquired the infection from unpasteurised camel milk. Traditionally, camel milk is consumed without being boiled due to the resulting unpleasant change in its taste. In addition to the easy accessibility of unpasteurised camel milk from street vendors, local customs of hospitality encourage the offering of unpasteurised camel milk to guests. One of the patients in the present study was an expatriate teacher who acquired the infection in this manner.

The majority of patients in the current study were male (73.4%). A high rate of brucellosis in men (80%) was also reported by Awaidy and Al Hashami.¹⁸ While this finding does not necessarily reflect acquisition through occupation as it does in other studies, it may reflect a higher rate of consumption of raw dairy products.²⁰ Overall, 75.5% of patients in the current study reported a history of consuming raw dairy products. El-Amin *et al.* reported a similar rate (63%) among infected children from Dhofar.²¹ In particular, one patient in the present study had consumed *kami*, a popular dairy snack produced in the Muscat and Al Batinah regions of Oman. *Kami* is a soft, sour, fermented dairy product which gradually becomes harder when stored at room temperature or refrigerated. Various studies have shown that while the milk fermentation process destroys *B. melitensis*, the *B. abortus* species is able to survive.^{22,23} As such, the possible acquisition of brucellosis through *kami* consumption could be due to the survival of the *B. abortus* species.

Animal exposure is another known method of acquiring zoonotic brucellosis.⁶ Levels of exposure can vary from actual caring for the animals to having them in the house or yard without being directly involved in their care. In the current study, only 25.9% of patients reported a history of animal contact. Much higher rates of animal exposure (83%) were reported in an earlier study by Awaidy and Al Hashami, possibly due

to differences in the populations studied.¹⁸ However, in cases in which patients denied both raw dairy product consumption and animal contact, one could question the safety of store-bought dairy products and the legitimacy of their pasteurisation claims. *Brucella* can survive in refrigerated temperatures of 4°C for up to six weeks in cream and 100 days in fresh soft cheeses.²² Another possibility is that patient history was not adequately obtained in certain cases, or that some patients were unwilling to disclose their history of raw dairy consumption due to the traditional belief that it could not possibly be a cause of illness. Alternatively, some patients may have simply forgotten instances of incidental or distant exposure to animals or infrequent consumption of raw dairy products.

Importantly, some cases in the current study demonstrated strong positive serology but negative blood cultures. This could be due to the insufficient volume of blood samples sent to the laboratory. Indeed, in some cases, blood culture sets sent on the same day for the same patient showed contradictory results. Therefore, in order to increase the chances of diagnosing brucellosis, it seems reasonable to send both serology and more than one set of blood cultures. Another interesting finding of the present study was the growth of *Brucella* from the synovial fluid of a patient with bilateral prosthetic joints in whom serology was negative and blood cultures were positive. It is not uncommon to find negative serology during chronic or relapsing infection phases, as SAT results tend to be falsely negative due to the switching from agglutinating to non-agglutinating antibodies.²⁴

A wide range of clinical features are observed among brucellosis patients, both in the current study and in reports from other countries.^{25–29} This clearly shows that signs and symptoms of brucellosis may vary extensively, ranging from non-specific manifestations to mimickers of other diseases. As such, it is paramount that this disease be considered during differential diagnosis. Fever was the most commonly reported symptom in the present study (95.2%) and often lasted longer than three weeks, reflecting the undulant nature of the disease. In contrast, a meta-analysis found that fever was only present in 78% of cases.²⁵ This indicates that fever may be absent in some cases presenting with non-specific symptoms.

Weight loss occurred in up to 51% of patients in the present study. Much lower rates of weight loss were reported in previous research (26.6–42%); this could be due to the inclusion of cases in which the reporting of weight loss relied on visual observation rather than objective measurement.^{25,26} Peripheral arthritis (excluding arthralgia) occurred in 12.5% of patients, with similar rates reported in neighbouring countries

(12–14.3%).^{26,27} However, there was a greater frequency of spondylitis/spondylodiscitis (12.5% versus 3.1%).²⁶ One of these patients was a young woman who had fallen during pregnancy, sustaining lumbar fractures which led to paraplegia. Although she had experienced lower back pain for months beforehand, she attributed this symptom to her pregnancy, thus delaying her diagnosis.

Various haematological abnormalities in the form of anaemia, leukopenia, leukocytosis and thrombocytopenia, including immune thrombocytopenic *purpura*, have been reported in brucellosis cases, of which the majority are mild and resolve with treatment.¹⁴ Leukocytosis—a symptom not reported in any of the patients in the current study—was found to occur infrequently in other studies (9–10.8%).^{26,27} Genitourinary system involvement occurred solely in 12.8% of male patients in the present study, in accordance with findings from previous studies (3.7–17.5%).^{13,26,28} One patient investigated for metastasising prostate cancer due to urinary symptoms, weight loss, lower back pain and high levels of prostate-specific antigen was tested for brucellosis due to a history of prolonged fever and consumption of raw dairy products. His serology was positive and all symptoms resolved upon treatment. Pulmonary involvement in the current study occurred at a slightly higher rate than that reported in the literature (7.8% versus ~6%), whereas the opposite was true for hepatosplenomegaly (10.9% versus 23%).^{25,29}

Relapses are documented in 5–30% of brucellosis cases, depending on treatment regimen and compliance to therapy; these typically occur within six months of discontinuation of therapy.³⁰ In the present study, relapses occurred in 10.9% of patients, two of whom once more consumed raw dairy products. One patient relapsed despite ceasing to consume raw dairy products and complying with therapy. In general, *Brucella* SAT titre levels are slow to drop after treatment; as such, this factor should not be considered indicative of treatment failure.³¹ An important issue in the prevention of brucellosis is that no human vaccines have yet been approved. While the RB51 animal vaccine was previously disseminated to animals in the Dhofar region, it was discontinued after 2010 due to complaints from camel herders that it caused miscarriages. Studies have confirmed that the live vaccine may cause abortions and premature births in pregnant dairy cows.^{32,33} Thus, the burden of prevention lies on raising public awareness and curtailing unsafe practices with regard to raw dairy consumption.

The current study highlights a number of important points regarding the risk factors,

epidemiology and presentation of human brucellosis in Oman. It is necessary that clinicians maintain a high index of suspicion of brucellosis due to its wide range of clinical presentations, many of which may be non-specific in nature or mimic other diseases. In addition, the study addresses the importance of obtaining a thorough history of risk factors and sending appropriate samples for diagnostic confirmation. Finally, while the findings show that the Dhofar region remains the primary geographical location of infections, other areas may also be at risk, particularly in the Al Batinah region.

This study was subject to certain limitations. In general, it is recommended that all samples and cultures containing *Brucella* isolates be processed in a class II biosafety cabinet (BSC) within a containment level 3 laboratory room or facility, while serology samples should be processed in a class II BSC.³⁴ However, as containment level 3 facilities for human microbiology diagnostic processes were not available in Oman during the study period, samples from suspected brucellosis cases were processed in a class II BSC within a containment level 2 laboratory. Moreover, identification of the precise causative *Brucella* species was limited to only a few patients in whom isolates showed unusual growth characteristics or from whom direct aspirate samples were tested by PCR. As such, the majority of isolates were identified solely to the genus level.

Conclusion

The majority of cases of zoonotic brucellosis infections observed in the present study were acquired as a result of the consumption of raw dairy products in Salalah. Due to the lack of a vaccine against *Brucella*, the best strategy to prevent infection appears to rely on public education initiatives regarding the dangers of raw dairy product consumption and exposure to animals. Informational campaigns should therefore be conducted over public media channels, particularly just before the start of the annual Khareef season when large numbers of tourists traditionally visit the Dhofar region.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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