

An Outbreak of Brucellosis: An Adult and Pediatric Case Series

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Background. Brucellosis is recognized as a neglected zoonotic disease and a major public health threat. The purpose of this study was to characterize epidemiological risk factors and healthcare utilization and compare clinical aspects of disease among adult and pediatric cases in North Texas.

Methods. A retrospective chart review of electronic medical records was completed at 3 large tertiary centers—Parkland Health and Hospital System, Clements University Hospital, and Children's Medical Center—between January 1, 2007 and June 1, 2017. Demographic, clinical, and laboratory variables were collected. Cases were defined as confirmed or probable.

Results. Twenty-eight cases of brucellosis were identified: 26 confirmed (9 children, 17 adults) and 2 probable cases (1 child, 1 adult). Half ($n = 14$) were diagnosed in 2016 during an outbreak in Dallas County. Risk factors associated with infection were consumption of unpasteurized cheese (71%), recent travel (54%), close contact to a confirmed human brucellosis case (36%), and exposure to animals (11%). Median days of symptoms was 10 and 16 for children and adults, respectively. The majority (79%) of patients visited the emergency department before diagnosis and 93% were hospitalized. Fever was the most common symptom in children (80%) and adults (100%). Hepatitis (75% of children) and anemia (82% of adults) were the most common laboratory abnormalities. The most common complication in children was splenic lesions (40%), and the most common complication in adults was hepato/splenomegaly (39%).

Conclusions. The diagnosis of *Brucella* infection requires a high index of suspicion and should be considered in patients presenting with a febrile illness and a compatible exposure history.

Keywords. *Brucella*; brucellosis; case series; outbreak.

Brucellosis is one of the most common zoonoses found globally and is caused by *Brucella* spp, a Gram-negative, facultative, intracellular bacteria [1, 2]. The disease is transmitted to humans via consumption of unpasteurized dairy products, direct contact with infected animals, inhalation of contaminated aerosols, and rarely human-to-human transmission [1, 3–5]. Brucellosis presents with nonspecific symptoms involving any organ and can be debilitating and disabling but rarely fatal [6]. Treatment of *Brucella* can be challenging, requiring multiple antimicrobials and having relapse rates of 5%–15% in uncomplicated disease [7]. The cost of human brucellosis includes not only the expense of diagnosis and treatment, but also the impact on lost work time. Analyses of mass vaccination of livestock for

brucellosis in endemic countries support these efforts as cost effective, including a significant impact on human health as measured by disability-adjusted life years [8].

Although eradicated in some developed countries, brucellosis is still endemic in certain regions of the world, including Mexico, parts of Central and South America, the Mediterranean basin, the Middle East, India, and North Africa. In the United States, incidence of human disease has significantly declined after implementation of eradication programs and milk pasteurization. Currently, brucellosis occurs more commonly in the US region bordering Mexico, such as Texas and California, with most cases resulting from consumption of unpasteurized dairy products from enzootic regions [9, 10]. Due to the relatively low numbers of US cases, many physicians are unfamiliar with brucellosis and inexperienced with diagnostic and therapeutic measures, which may result in delays in recognition of disease, inadequate treatment, increased complications, and unnecessary healthcare costs.

In recent years, a small number of US case series from Texas [11–13] and Chicago [14] have been published that focused on describing risk factors and clinical and laboratory features. However, the impact of disease on patients and the healthcare system are not entirely understood, and there are limited data

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available on missed opportunities for diagnosis of human brucellosis in the United States. This study characterizes the epidemiological risk factors that led to a brucellosis outbreak in Dallas, Texas and compares the diagnostic and therapeutic approaches in pediatric and adult patients over 10 years. Furthermore, we assess the extent of healthcare resource utilization by these patients and highlight some missed opportunities for diagnosis at our institutions.

METHODS

A retrospective chart review of electronic medical records was completed at 3 large tertiary centers between January 1, 2007 and June 1, 2017: Parkland Health and Hospital System, Clements University Hospital, and Children's Medical Center. The study protocol was approved by the UT Southwestern Medical Center Institutional Review Board. Cases were identified by *International Classification of Diseases, Ninth Revision* (ICD9) code 0.23 and/or ICD10 code A23. Cases were classified as either probable or confirmed as per the brucellosis 2010 Council of State and Territorial Epidemiologists case definitions [15, 16]. Confirmed *Brucella* infection was defined as a clinically compatible illness with isolation of the pathogen from a clinical specimen or a 4-fold rise in *Brucella* antibody titers between acute- and convalescent-phase sera obtained ≥ 2 weeks apart. Probable brucellosis was defined as a clinically compatible illness with an epidemiological link to a confirmed human or animal case and/or presumptive laboratory evidence. Presumptive laboratory evidence of *Brucella* included positive *Brucella* polymerase chain reaction (PCR) testing and/or *Brucella* serum agglutination test $\geq 1:160$. Demographic (eg, age, gender, race/ethnicity), epidemiologic (eg, travel within past 6 months, food exposure, sick contacts), and clinical data were collected for all subjects. Clinical variables included past medical history, associated symptoms, duration of symptoms before diagnosis, emergency department (ED) visits, and admissions related to brucellosis. Length of hospitalization was calculated only for initial episodes and did not include admissions due to relapses. Duration of bacteremia (calculated only for initial events) was the duration from the first positive culture to the last positive culture. The number of positive blood cultures per person and the time to positivity (TTP) were also identified. Complete blood count and renal and liver function tests were reported, as well as human immunodeficiency virus status, if tested. Radiographic findings, including echocardiography results, were also collected. As described in previous studies, relapse was defined as reappearance of signs or symptoms after an asymptomatic period and completion of therapy with or without bacteremia [17–19].

Frequencies of all binary and categorical variables were described, and, for continuous variables, median with interquartile range were calculated. Data were stratified by adult (≥ 18 years old)

and pediatric (<18 years old) groups. All data analyses were completed using StataSE 15 (StataCorp LLC, College Station, TX).

RESULTS

Demographic Characteristics of Patients With Brucellosis

A total of 151 charts were reviewed (107 adult charts and 44 pediatric charts), among which 28 *Brucella* cases were identified: 26 confirmed (9 children, 17 adults) and 2 probable cases (1 child, 1 adult). Ages ranged from 3 to 75 years with a median age of 11 years for pediatric patients and 49 years for adult cases. All patients were of Hispanic ethnicity, except for 1 child who was non-Hispanic white (Table 1). Half of all cases ($n = 14$) occurred in 2016, corresponding with an outbreak of brucellosis in Dallas County (Figure 1).

Risk factors included consumption of unpasteurized cheese in 71% ($n = 20$) of cases, recent international travel in 54% (all but 1 to Mexico) of cases, family member/close contact with brucellosis in 36% ($n = 10$) of cases, no identifiable risk factor in 18% ($n = 5$) of cases, and exposure to animals in 11% ($n = 3$) of cases. The 1 case of *Brucella canis* infection reported caring for a dog with spontaneous abortions (Table 1).

Signs and Symptoms of Brucellosis Patients

The most common presenting symptom was fever in both children and adults. Constitutional symptoms (night sweats, weight loss, anorexia, myalgia) occurred in 61% of adults but only 30% of the pediatric cases. An equal percentage (44%) of

Table 1. Demographics and Risk Factors

	Pediatrics n = 10 (%)	Adults n = 18 (%)
Characteristics		
Age, Years, Median		
Median [IQR]	11 [8–14]	49 [35–55]
Gender		
Male	3 (30)	10 (5)
Race/Ethnicity		
Hispanic	9 (90)	18 (100)
White	1 (10)	0 (0)
Insurance		
Yes	9 (90)	4 (22)
Visited ED Before Diagnosis		
Yes	8 (80)	14 (78)
Admission to Hospital		
Yes	10 (100%)	16 (89%)
Median days of hospitalization [IQR]	11 [8–15]	7 [3–12]
Recent Travel		
Yes	6 (60)	9 (50)
Exposure (Can Have More Than One)		
Consumption of unpasteurized cheese	5 (50)	15 (83)
Animals (farm, domestic)	1 (10)	2 (11)
Family member/close contact with brucellosis	4 (40)	6 (33)
Unknown	3 (30)	2 (11)

Abbreviations: ED, emergency department; IQR, interquartile range.

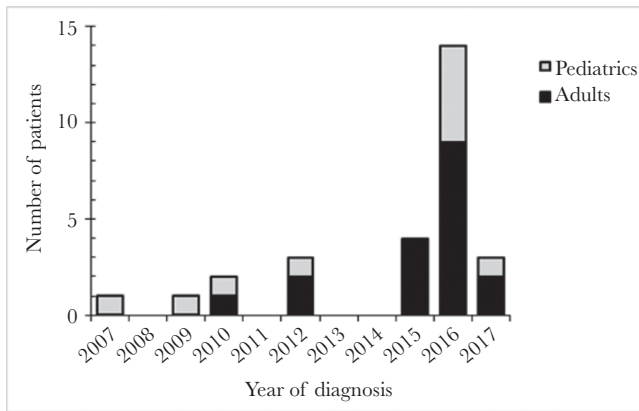


Figure 1. Distribution of brucellosis cases according to year of diagnosis.

adult patients complained of gastrointestinal (GI) symptoms, musculoskeletal symptoms, and neurological symptoms. The second most common presenting symptoms in children were GI-related, followed by neurological and musculoskeletal. Testicular pain was a presenting symptom in 2 adult males, but no pediatric patients presented with reproductive organ involvement. Rash was noted in 2 pediatric patients (Table 2).

Duration of symptoms before diagnosis of brucellosis varied but overall ranged from 1 day to up to 4 months (Table 2). The median duration of symptoms was 10 and 16 days for children and adults, respectively. It was more common for adults to present with prolonged symptoms of weeks to months. The

Table 2. Clinical Signs and Symptoms

Sign/Symptom	Pediatrics n = 10 (%)	Adults n = 18 (%)
Presenting Symptoms		
Subjective fevers	8 (80)	18 (100)
GI symptoms (abdominal pain, vomiting, diarrhea)	5 (50)	8 (44)
Neurological (headache, dizziness, weakness)	4 (40)	8 (44)
Musculoskeletal pain (back, joint pain/swelling)	4 (40)	8 (44)
Testicular pain	0 (0)	2 (11)
Constitutional symptoms (night sweats, malaise, wt loss, myalgia)	3 (30)	11 (61)
Rash	2 (20)	0 (0)
Duration of Symptoms		
Median days [IQR]	10 [7–42]	16 [10–45]
Imaging/Complications		
Hepato/splenomegaly	3 (30)	7 (39)
Endocarditis	0 (0)	1 (6)
Osteomyelitis/discitis/arthritis	3 (30)	2 (11)
Orchitis	1 (10)	2 (11)
Splenic lesions	4 (40)	3 (17)
Neurobrucellosis	2 (20)	1 (6)
Relapse	2 (20)	2 (11)

Abbreviations: GI, gastrointestinal; IQR, interquartile range; wt, weight.

longest duration of symptoms was 120 days in an adult female patient. Overall, 8 (80%) children and 14 (78%) adults were examined in an ED due to their symptoms and discharged home without a diagnosis of brucellosis. Three children visited the ED twice and 1 child was examined 3 times before establishing the diagnosis. Of the adults, 4 of 18 were admitted on their initial encounter and the remaining were seen once in the ED. Of these, 8 were called back due to positive cultures, and the other 6 returned due to persistent symptoms. Two patients (1 adult, 1 child) were admitted to the hospital and discharged home with other diagnoses. All children were admitted to the hospital with a median length of stay of 11 days. The majority of adults (n = 16, 89%) were hospitalized, with a median length of stay of 7 days. In addition, 78% (n = 14) of adults were uninsured, whereas only 1 pediatric patient was uninsured.

Laboratory and Radiographic Findings in Brucellosis Patients

Laboratory abnormalities are detailed in Table 3. Anemia was the most common laboratory abnormality observed in adults, and elevated aspartate aminotransferase/alanine aminotransferase was most commonly seen in children. Human immunodeficiency virus testing was performed in 4 children and 15 adults; all results were negative.

Brucella titers were available for review in only a minor subset of our patients. Serum agglutination tests were positive in all those tested: 8 adults and 2 pediatric patients. Blood *Brucella* PCR was detectable in an adult patient who was also later found to be bacteremic (Table 3).

Table 3. Laboratory Findings

Laboratory Abnormalities	Pediatrics	Adults
	No./Total No. (%)	No./Total No. (%)
AST >50 units/L	6/8 (75)	11/15 (73)
ALT >50 units/L	6/8 (75)	8/15 (53)
Alkaline phosphatase >140 units/L	5/8 (63)	7/15 (47)
Total bilirubin >1.3 mg/dL	0/8 (0)	2/15 (13)
Leukopenia (WBC <4.0 × 10 ⁹ /L)	2/10 (20)	4/17 (24)
Anemia for age	4/10 (40)	14/17 (82)
Thrombocytopenia (platelets <150 × 10 ⁹ /L)	1/10 (10)	6/17 (35)
Diagnostic Testing		
Positive Serological Testing		
Serum agglutination test	2/2 (100)	8/8 (100)
Positive <i>Brucella</i> PCR		
Blood	0/0 (0)	1/1 (100)
Bacterial cultures n = 10 (%) n = 18 (%)		
Positive Culture		
<i>Brucella melitensis</i>	8 (80)	17 (94)
<i>Brucella canis</i>	1 (10)	0 (0)
Median number of positive cultures/person [IQR]	3 [2–3]	3 [2–4]
Median duration of bacteremia (days) [IQR]	6 [4–10]	2 [1–6]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; PCR, polymerase chain reaction; WBC, white blood cells.

Of the confirmed cases, *Brucella melitensis* was isolated from specimens in all patients, except for 1 pediatric case with *B canis* bacteremia. *Brucella melitensis* was found in both synovial fluid and blood culture in 1 child who presented with septic arthritis of the hip. One adult with 3 months of back pain was found to have discitis with a large epidural abscess that was culture positive for *B melitensis*, but no bacteremia was detected. The median TTP of blood cultures was 85 hours in children, slightly longer than in adults (78 hours) (Figure 2). *Brucella* was isolated at 233 hours after collection in 1 boy in which the blood culture was held for >5 days. Prolonged bacteremia was often noted in those patients who had repeat blood cultures. The median number of positive cultures for each patient was 3. The median length of bacteremia was 6 days in children and 2 days in adults (Table 3).

Hepatosplenomegaly was the most common radiographic finding in all ages. Osteoarticular disease was observed in 3 children and 2 adults. Echocardiography was performed in 5 children and 16 adults, but no vegetations were visualized. A female adult was diagnosed with spondylitis, reported to be noncompliant with treatment, and readmitted due to a new heart murmur and thickened aortic valve but no vegetations on transesophageal echocardiography. She was treated for presumed *Brucella* endocarditis. Orchitis was a presenting symptom in 2 adult males and reported as a manifestation of relapsed disease in a teenaged boy. Splenic lesions were demonstrated in 7 patients. Neurobrucellosis was diagnosed in 2 pediatric patients and 1 adult. Two adults and 2 children were found to have relapsed disease, and 3 of the 4 patients presented with recurrence of bacteremia (Table 2).

Treatment Regimens in Brucellosis Patients

In the pediatric cases, the most common treatment regimen was combination 3-drug therapy with gentamicin, doxycycline, plus rifampin ($n = 6$) (Figure 3). One child who was 3 years of age received trimethoprim-sulfamethoxazole in place of doxycycline, along with rifampin and gentamicin. Gentamicin was generally administered for the first 7–10 days of therapy. Adults were largely treated with doxycycline and rifampin ($n = 9$), and 5 adults received 3-drug therapy with doxycycline, rifampin, and gentamicin.

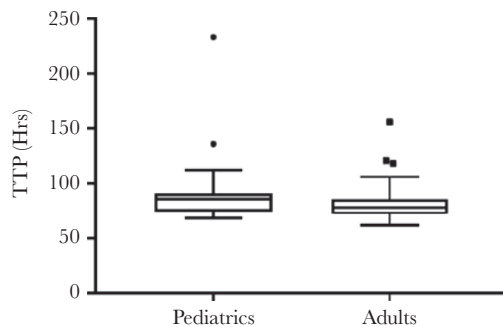


Figure 2. Time to positivity (TTP) in hours of bacterial blood cultures.

DISCUSSION

We present a 10-year combined adult and pediatric case series that reflects one of the largest and comprehensive *Brucella* experiences described in the United States. A total of 28 brucellosis cases are reported: 26 confirmed (9 children, 17 adults) and 2 probable cases (1 child, 1 adult). Both probable cases presented with a clinically compatible illness and positive serum agglutination tests. The majority of cases were associated with consumption of unpasteurized cheese, international travel, or close contact with another individual who was infected. On multiple occasions (79%), individuals who were subsequently diagnosed with brucellosis were sent home from the emergency room with alternative diagnoses, resulting in delays in treatment.

Human brucellosis in the United States has shifted to be primarily a foodborne illness related to unpasteurized goat milk products contaminated with *B melitensis*, which is consistent with the findings of this study [20]. We observed an increase in *Brucella* cases in 2016–2017, and, of these, 100% of all confirmed cases were attributed to *B melitensis*. Per the Dallas County Health and Human Services (DCHHS), there were 20 confirmed and 5 probable cases in Dallas county in 2016, 14 of which presented to our affiliated hospitals [21]. In this study, all cases in 2016 were among Hispanic individuals, and the majority of cases (71%) were linked to consumption of unpasteurized goat cheese. Several patients with confirmed brucellosis denied consumption of unpasteurized cheese or other identifiable risk factors but were relatives of human cases. This could be explained by the findings of DCHHS upon case interviews where 67% of the patients were unaware that the consumed cheese was unpasteurized, suggesting that individuals failed to report ingestion of unpasteurized cheese simply because they were uninformed [21]. A study by Nguyen et al [22] reported that 57% of border crossers that imported cheese reported the cheese to be pasteurized, 27% were unsure of pasteurization, and only 16% reported that the cheese was unpasteurized. In our 10-year review, it was observed that approximately half of our patients reported no recent travel, which is less than other US studies [11, 14]. It is important to recognize that imported unpasteurized cheese is often shared with family and friends and/or sold locally in the United States, and, therefore, absence of travel should not rule out brucellosis in the differential diagnosis. These findings emphasize the need to obtain a detailed history of exposures (both local and international) to properly assess for brucellosis risk factors.

Brucellosis is able to mimic a myriad of human diseases leading to incorrect diagnoses or delays in diagnosis [6]. One aim of this study was to examine healthcare utilization by our patients and to identify missed opportunities for timely diagnosis and treatment of brucellosis. We report a significant number of admissions, 93% total, with an average length of stay of 12 and 10 days for children and adults, respectively. Furthermore, a large percentage of patients (8 children, 14 adults) visited

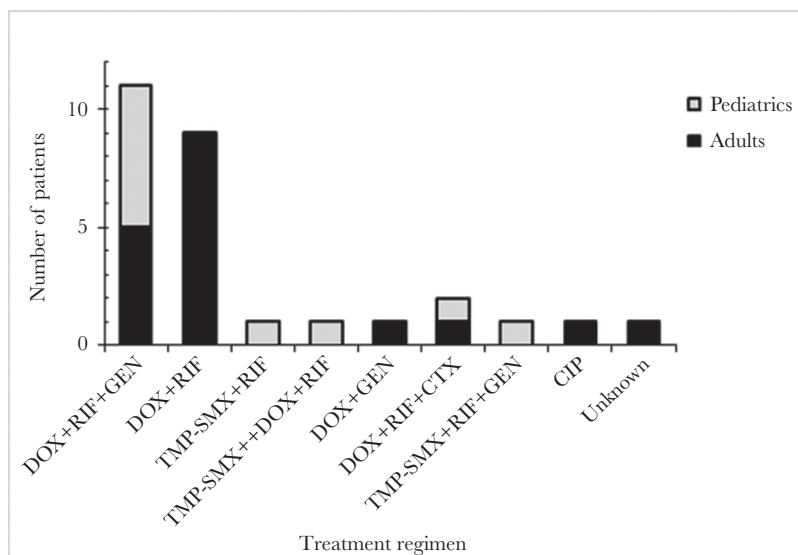


Figure 3. Antibiotic regimen used to treat brucellosis. CIP, ciprofloxacin; CTX, ceftriaxone; DOX, doxycycline; GEN, gentamicin; RIF, rifampin; TMP-SMX, trimethoprim sulfamethoxazole.

the ED and were discharged home with other diagnoses, but *B melitensis* was isolated from blood cultures obtained during ED visits in 4 children and 8 adults. Those patients in whom blood cultures or *Brucella* titers were not initially sent revisited the ED due to persistent symptoms, with 1 woman presenting 25 days after her initial encounter. One teenager and an adult were misdiagnosed with infectious mononucleosis and urinary tract infection, respectively, leading to multiple hospital visits until the diagnosis was finally reached. In addition, over half (54%) of patients in our study were uninsured, leading to increased costs to patients and the healthcare system. Data from the DCHHS estimated personal economic losses at a median of \$4000 per person [21].

Brucellosis presents with a wide range of symptoms and can involve almost any organ, as demonstrated in this study [23]. The most common presenting symptom was fever, as previously described in the literature [1, 6]. Overall, adults and children presented similarly, although constitutional and genitourinary symptoms were more common in adults. Our observations were comparable to previous reports with some minor differences. We found that 46% of patients presented with GI symptoms (abdominal pain, diarrhea, vomiting), whereas others reported lower percentages of 13%–24% [14, 20, 24]. A lower number of children presented with constitutional symptoms in this study; however, this variability is recognized in the literature [6, 25]. Neurological complaints were slightly more common in our study in comparison to previous case series, although other studies only recorded headaches and not other neurologic symptoms [14, 20, 26, 27]. The mean duration of symptoms before diagnosis was more prolonged for adults (35 days) versus children (20 days), which is consistent with studies from endemic areas. Pediatric studies from Greece reported a mean

duration of symptoms of 13.4–16.3 days [24, 27, 28], and reports from other endemic areas that included adults described higher means of up to 44 days [18, 29]. As for laboratory findings, we detected hepatitis more commonly in children and hematological abnormalities more often in adults. Although this was observed in this study, it is evident from previous reviews that similar laboratory findings occur at various magnitudes. A US study found rates of anemia as high as 65% in children, whereas 20%–53% of the international population was anemic [14, 24, 30, 31].

Duration of bacteremia is infrequently reported in the literature, but Logan et al [14] described a median length of 2.5 days in children. We observed a longer median duration of bacteremia in children in our study (6 days), which may be due to the practice of repeating blood cultures until clearance by the pediatricians. Prolonged *Brucella* bacteremia despite clinical improvement in children was not associated with unidentified foci of infection or inadequate antibiotic therapy in our study. Largely, cultures were only repeated in adults where diagnosis was unknown, and *Brucella* was not yet isolated from cultures, although bacteria were detected fairly quickly at 3–4 days of growth. Of note, because newer blood culture media and automated systems have improved TTP over prior culture techniques, holding blood culture bottles for extended durations is not necessary [32].

Complications with focal disease were found more frequently in adults than children. The most common complications of all ages were osteoarticular infections and splenic lesions. Osteoarticular complications included sacroiliitis, hip arthritis, epidural abscess, and spondylitis. Neurobrucellosis is described to occur in 2%–5% of brucellosis patients [33]. In this study, we found a somewhat higher rate of ~11%, with most patients

presenting with meningioencephalitis and/or psychiatric manifestations. We report a total of 4 cases that relapsed (22%), and we failed to identify any shared risk factors among those that relapsed.

Our study has several limitations. First, we performed a retrospective chart review and were therefore dependent on information available through electronic medical records. However, epidemiological links were compared with data from DCHHS's case interviews and were found to be similar. Second, although this study included data from 3 large tertiary centers, this is not a comprehensive summary of the local 2016–2017 *Brucella* outbreak because other hospitals in Dallas county that treated patients during this time were not included in our study. Third, some patients were followed by their primary care physician after hospitalization and not by our infectious diseases clinics or other affiliations, therefore the number of patients that were lost to follow-up is unknown. Accordingly, the true number of complications may be underestimated in this study. Finally, there were missing laboratory features for some cases because investigations varied among patients. Nonetheless, we describe in detail the clinical findings, complications, treatment outcomes, and healthcare utilization of patients with brucellosis over a 10-year period, including a recent outbreak, and involving a broad range of ages and presentations. Specifically, we highlight key missed opportunities for early diagnosis of disease and opportunities for educating both medical providers and the general population about the public health threat of this zoonotic infection.

CONCLUSIONS

Brucellosis can be debilitating and disabling with its diverse spectrum of disease, chronicity, need for prolonged therapy, and high relapse rates. This infection is often misdiagnosed, leading to delays in therapy and increased risk of complications. A key element to improved early disease recognition is understanding and asking about risk factors including local as well as imported unpasteurized cheese consumption and assessment of symptoms among close family members. The current study represents one of the largest contemporary case studies describing brucellosis in the United States. Although not endemic in the United States, the diagnosis of *Brucella* infection requires a high index of suspicion and should be considered in patients presenting with a febrile illness and a compatible exposure history.

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