Human Brucellosis

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Background: **Human brucellosis has a serious medical impact worldwide, and its eradication poses major difficulties. Although human brucellosis is relatively rare in the United States (approximately 100 cases per year), there is concern that this disease is largely underdiagnosed and underreported. Additionally, immigrants from endemic areas are arriving to this country, and *Brucella* species are considered to be biologic agents for terrorism. Human brucellosis affects all age-groups, and family physicians are not well versed in recognizing and treating this potentially life-threatening condition.**

Methods: **A literature review from 1975 to 2001 was performed using the key words "human brucellosis," "zoonosis," and "bioterrorism."**

Results and Conclusions: **Appropriate antimicrobial therapy and duration of treatment of human brucellosis will reduce morbidity, prevent complications, and diminish relapses. Because of the nonspecific symptoms and rarity of human brucellosis in the United States, family physicians must acquire a detailed dietary and occupational history to diagnose the disease promptly. Family physicians must assume a responsible role in reporting this disease, as well as be aware of persons at high-risk for this disease and the potential sources of infection. (J Am Board Fam Pract 2002;15:401–6.)**

Human brucellosis is a potentially life-threatening multisystem disease. Rarely reported in the United States, human brucellosis is a zoonotic disease of bacterial origin. The first case was reported in the United States in 1898 by Musser and Sailer, and reported cases reached a maximum of 6,321 in 1947.[1] Since that time, there has been a steady decline. The Centers for Disease Control and Prevention (CDC) reported approximately 100 cases each year during the past 10 years, with most cases in the southwest region.[2] The decline in disease incidence is mainly due to compulsory pasteurization of milk and to the control of the disease in dairy cattle.[3] Worldwide, this disease has a major presence in the Middle East, southern Europe, and South America (ie, Brazil, Columbia). Studies have shown that in the United States human brucellosis is underdiagnosed and underreported. The reporting rate in some states, ie, California, has been as low as 10%.[1]

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Methods

A literature review was performed using the key words "human brucellosis," "zoonosis," and "bioterrorism," dating from 1975 to 2001. A case report on human brucellosis is described.

Case Report

An 8-year-old girl complained of a 2-week history of a severe sore throat, fever, abdominal pain, anorexia, and a 5-pound weight loss. Eight days earlier she had immigrated with her parents from Syria, where she recently had been given a 4-week course of trimethoprim-sulfamethoxazole for an apparent food-borne illness. She completed the antibiotic approximately 2 weeks before the onset of the latest symptoms.

The patient's medical history was remarkable only for rheumatic fever. She had no history of surgery and no known drug allergies. Her birth was without incident, and her immunizations, which included the BCG vaccine, were up to date. She had been born in Iraq and moved with her parents and three siblings to Syria, where she lived on a farm. A detailed dietary history showed she consumed unpasteurized goat's milk.

At admission to the hospital the patient was febrile (102.0°F [38.9°C]), tachycardic (108 beats per minute), slightly tachypneic (24/min), and nor-

Table 1. Admission Laboratory Results.

Laboratory Test	Value
Prothrombin time	21.2 sec
Partial thromboplastin time	53.8 sec
Fibrinogen	785 mg/dL (7.85 g/L)
Bicarbonate	21 mEq/L (mmol/L)
Chloride	99 mEq/L (mmol/L)
Blood urea nitrogen	12 mg/dL (4.28 mmol/L)
Creatinine	0.5 mg/dL (44.2 μmol/L)
Glucose	89 mg/dL (4.94 mmol/L)
Amylase	50 U/L
Total protein	5,600 mg/dL (56 g/L)
Serum aspartate aminotransferase	257 U/L
Serum alanine aminotransferase	94 U/L
Alkaline phosphatase	173 U/L

motensive (90/48 mm Hg.). She appeared acutely ill but nontoxic, and her oral mucosa was dry. Her tympanic membranes were normal, her oropharynx was erythematous, and her tonsils were swollen (2+) but without exudate. Her neck had full range of motion, and there was diffuse cervical adenopathy. Her abdomen was not distended, but it was diffusely tender, chiefly in the right upper quadrant, where the liver was palpated 5 cm below the costal margin, and in the left upper quadrant, where the spleen was palpated 4 cm below the costal margin. Findings of neurologic and dermatologic examinations were normal. The lungs were clear to auscultation, and no murmurs, rubs, or gallops were heard during her heart examination.

Laboratory findings at admission showed the following values: leukopenia (white cell count 2.1×10^9/L), anemia (hemoglobin 9.9 g/L), thrombocytopenia (platelets 118×10^9/L), and hypoalbuminemia (albumin 25 g/L). Other pertinent results are displayed in Table 1.

An echocardiogram showed a small pericardial effusion but no valvular disease. A bone marrow biopsy showed evidence of noncaseating granulomas consistent with brucellosis. Positive blood cultures showing gram-negative bacilli consistent with *Brucella melitensis* infection confirmed the diagnosis. Serum agglutination test for *B melitensis* was 1/160, and the erythrocyte sedimentation rate was 6 mm/h. A Monospot test was negative, and throat and urine cultures were normal.

Initially the patient was given intravenous trimethoprim-sulfamethoxazole and rifampicin for presumptive diagnosis of human brucellosis until it was confirmed. Throughout her hospital course the patient's pancytopenia worsened. This condition was probably drug induced and not due to the infection. To avoid further bone marrow suppression caused by trimethoprim-sulfamethoxazole, the antibiotic regimen was changed to the combination of rifampicin with doxycycline and gentamicin. After consultation with a hematologist and infectious disease specialist, it was recommended that she be given intravenous rifampin and gentamicin for 5 days and then complete a total of 45 days of oral rifampin and a 45-day course of oral doxycycline. Her age of 8 years allowed for the use of doxycycline without dental concerns.

By the ninth day of admission, repeated blood cultures showed that her bacteremia had resolved. Her fever subsided, and findings from a second echocardiogram were normal. She was released from the hospital to complete 45 days of oral rifampicin and doxycycline and was symptom-free with no signs of relapse at 3-month and 6-month follow-up examinations.

Discussion

This patient had a case of acute human brucellosis caused by *B melitensis* infection. There are six *Brucella* species, four of which are known to infect humans: *B melitensis*, *B abortus*, *B suis*, and *B canis*. *B abortus* is found principally in cattle; *B melitensis*, in goats and sheep; *B suis*, in swine; and *B canis*, in kennel-raised dogs. *B canis* is the least common cause of human brucellosis, and most infections of *B canis* have been acquired in the laboratory.[4]

Human brucellosis is common in many parts of the world but not in the United States. The true incidence is unknown, although in the United States the CDC reports fewer than 0.05 cases per 100,000 population, with most being reported from Texas, California, and Illinois. During the past 10 years, approximately 100 cases per year have been reported in the United States.[2] Human brucellosis is widespread in the Middle East. Epidemiologic studies in such areas as southern Saudi Arabia have shown that 19.2% of that population had serologic evidence of exposure and 2.3% had active disease.[5] Several other bacterial diseases are transmitted by farm animals to humans (Table 2).

Brucellosis is a multisystem disease with a broad spectrum of nonspecific symptoms that generally

Table 2. Bacterial Diseases Transmitted by Farm Animals.

Disease and Organism	Common Farm Animal Source	Means of Spread
Brucellosis (*Brucella* species)	Cattle, goats, sheep, swine	Direct contact with birth products, ingestion of milk, inhalation of aerosols
Campylobacteriosis (*Campylobacter jejuni*)	Poultry	Ingestion of contaminated food, direct contact
Hemolytic-uremic syndrome (*Escherichia coli* 0157:H7)	Cattle	Ingestion of contaminated food or water
Leptospirosis (*Leptospira* species)	Livestock	Contact with urine, particularly in contaminated water
Salmonellosis (*Salmonella* species)	Poultry	Ingestion of contaminated food, direct contact
Tetanus (*Clostridium tetani*)	Any animal, usually indirect, via soil	Wound infection, contaminated bite
Yersiniosis (*Yersinia enterocolitica*)	Swine	Ingestion of contaminated food or water, rarely direct contact
Anthrax (*Bacillus anthracis*)	Goats, sheep, cattle, swine, horse, buffalo, deer	Contact with infected animals or their contaminated products

Adapted from *2000 The Red Book: Report on the Committee on Infectious Diseases.* 25th edition. Elk Grove Village, Ill: American Academy of Pediatrics, 2000:773–4.

occur within 2 weeks (but sometimes up to 3 months) after inoculation. Because the clinical illness is nonspecific, a thorough history, including a detailed dietary history, is crucial. Treatment of brucellosis must control the acute illness and prevent its potential complications and relapse. This particular case developed as a result of consuming unpasteurized, contaminated goat's milk that had been infected with *B melitensis*. These gram-negative, aerobic non–spore-forming coccobacilli are free-living, soil-dwelling organisms that can infect goats and sheep. In infected humans, the bacteria have intracellular localization, particularly within the reticuloendothelial system.

Another factor contributing to the clinical condition of our patient was a course of antibiotics that had been prescribed for too short a period. Studies support that relapses are not uncommon as a result of therapy discontinued prematurely.[6] Most relapses occur within 3 to 6 months of stopping therapy.[7,8]

The patient had many of the acute signs and symptoms of human brucellosis, ie, undulating fever, myalgia (Table 3), and other clinical manifestations such as splenomegaly, hepatomegaly, and spondylitis[9] (Table 4). Infective endocarditis,[10] although rare, is the most devastating complication from systemic brucellosis and could require surgi-

Table 3. Signs and Symptoms of Human Brucellosis.

Anorexia
Back pain
Cephalgia
Fatigue
Fever
Malaise
Myalgia
Sweats
Weight loss

Adapted from The Centers for Disease Control.[2]

Table 4. Clinical Manifestations of Human Brucellosis.

Anemia
Deep vein thrombosis
Endocarditis
Hepatomegaly
Leukocytoclastic vasculitis
Leukopenia
Liver abscess
Lymphadenopathy
Meningitis
Nephritis
Optic neuritis
Pancytopenia
Papilledema
Splenic abscess
Splenomegaly
Spondylitis
Thrombocytopenia
Uveitis

Adapted from Solera et al,[9] Cohen et al,[10] Vallejo et al,[11] Colmenero et al,[12] Odeh et al,[13] Nagore et al,[14] Mousa et al,[15] Odeh and Oliven,[16] Abd Elrazak et al,[17] Walker et al,[18] and Crosby et al.[19]

Table 5. Sensitivity and Specificity of Diagnostic Tests for Human Brucellosis.

Test	Acute Brucellosis		Chronic Brucellosis	
	Sensitivity	Specificity	Sensitivity	Specificity
Blood and bone marrow culture	53	100	5	100
Serum agglutination test: titer ≥ 160	92	100	45	100
Enzyme-linked immunosorbent assay				
IgG ≥ 1,600 mg/dL	98	98	100	98
IgM ≥ 100 mg/dL	100	36	82	36
IgA ≥ 100 mg/dL	99	89	89	100
Polymerase chain reaction	Not available	Not available	Not available	Not available
Western blot	Not available	Not available	Not available	Not available

Adapted from Araj et al.[21]

cal intervention.[20] Splenic,[11] liver,[11] and pulmonary abscesses can occur. Lymphadenopathy is found in 10% to 20% and splenomegaly or hepatomegaly in 20% to 30% of cases.[12] Other rare conditions include deep vein thrombosis,[13] leukocytoclastic vasculitis,[14] meningitis,[15] and nephritis.[16] Ocular manifestations include optic neuritis,[17] papilledema,[18] and uveitis.[18]

The diagnosis (Table 5) of this condition centers on a detailed history and isolation of the organism, for which the blood cultures are still the standard method.[22] Blood and bone marrow cultures are most often positive during the acute phase.[23,24] The erythrocyte sedimentation rate is of little diagnostic value.[25] Common hematologic findings include leukopenia, anemia, and thrombocytopenia.[19]

Other body materials, such as cerebrospinal fluid, can be examined when there are central nervous system symptoms. Bone marrow biopsies, as well as liver and lymph node biopsies, typically show noncaseating granulomas. Other diagnostic tests for most of which the sensitivities and specificities have been established include enzyme-linked immunoabsorbent assay (ELISA), polymerase chain reaction, serum agglutination test, and Western blot.[21] The predictive values are displayed in Table 5. The ELISA test for *Brucella* antigen detection has shown to be an acceptable alternative to blood culture for the diagnosis of brucellosis.[26] If the serum agglutination test result is equivocal, the ELISA test can give a definitive diagnosis.[27] Polymerase chain reaction is also under evaluation for more effective typing methods.[28] Western blot testing can be useful to differentiate acute from past subclinical infection.[29]

The standard treatments (Table 6) for these patients vary depending on the patient's age and pregnancy status.[30] Regardless of the type of combination therapy, no statistically significant difference was found regarding early clinical response in human brucellosis.[35] Recommended treatment is as follows: for children younger than 8 years, a combination therapy of trimethoprim-sulfamethoxazole and aminoglycoside[31] or a combination of rifampicin and trimethoprim-sulfamethoxazole for 45 days[33]; for those aged 8 years and older, a combination of doxycycline and rifampin[32] or a second option of rifampicin and gentamicin.[33] Rifampicin combined with ciprofloxacin for 30 days has also

Table 6. Treatment of Human Brucellosis.

Stage of Life	Treatment Option 1	Treatment Option 2	Treatment Option 3
Pregnancy	Rifampicin 900 mg po qd for 6 wk		
<8 years	Trimethoprim-sulfamethoxazole (TMP-SMX) 5 mg/kg of TMP q12 h po for 45 d + gentamicin 2 mg/kg iv or im for 7 d	TMP/SMX 5 mg/kg of TMP q12 h po for 45 d + rifampicin 10 mg/kg/d po qd for 45 d	
≥8 years and adults	Doxycycline 100 mg po bid for 6 wk + rifampicin 600–900 mg/d po for 6 wk	Gentamicin 2 mg/kg q 8 h iv or im for 7 d + rifampicin 600–900 mg/d po qd for 6 wk	Ciprofloxacin 1 g po qd for 30 d + rifampicin 600 mg po qd for 30 d (adults only)

Adapted from Figueroa Damian et al,[30] Lubani et al,[31] WHO,[32] Solera et al,[33] and Agalar et al.[34]

been shown to be effective and offers the advantage of a shorter treatment duration.[34] In children, rifampicin monotherapy, which is not recommended, can be used, but single-drug treatment is discouraged because it is associated with a high relapse rate.[36]

Prevention of human brucellosis focuses mainly on elimination of infection in hosts (ie, goats, cows), along with hygiene, vaccine, and effecting heating of dairy products and related foods. In many cases, human brucellosis can be an occupational hazard for veterinarians, abattoirs, farmers, and dairy workers. Because contact with infected materials can allow organisms to enter through skin lesions and gain access to the lymphatic system, hygienic precautions are important. Vaccines developed to prevent this disease in humans have had limited efficacy and have been associated with serious medical reactions.[37,38] Vaccines developed to prevent and control livestock infection are effective in reducing the incidence of human brucellosis. Most veterinary vaccines focus on *B abortus* and *B melitensis*.[39] *Brucella* species have also been viewed as potential biological threats for terrorist-related activities.[40] The organism could be delivered as a slurry in bomblets or, theoretically, as a dry aerosol.

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